IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of

Anderson	Confirmation No. 4972
Serial No. 10/788,413	Group Art Unit 1617
Filed March 1, 2004	Examiner Wang

For TREATMENT USING DANTROLENE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF BARBARA W. BRANDOM UNDER 37 C.F.R. 1.132

1. I am a Board Certified Anesthesiologist, with a specialty in Pediatric Anesthesiology, and practice anesthesiology at Children's Hospital of Pittsburgh and Presbyterian-University Hospital in the University of Pittsburgh Medical Center, and have practiced anesthesiology there since 1980.

2. I am a Professor of Anesthesiology at the University of Pittsburgh School of Medicine and among my responsibilities are teaching in the anesthesiology resident program, and training anesthesiologists in, among other things, recognition and treatment of anesthesia induced malignant hyperthermia ("MH").

3. For several years I have volunteered my time and efforts on behalf of the Malignant Hyperthermia Society of the United States (MHAUS), specifically: (i) I am now and since 2000 have been the Director of the North American Malignant Hyperthermia Registry, the world's largest database of case reports of anesthesia induced malignant hyperthermia episodes and treatment thereof; and, (ii) I serve as one of the MHAUS MH Crisis Hotline consultants, and in this capacity I take calls for two weeks each year from and counsel clinicians around the United States in the recognition and treatment of the MH cases as they are occurring; (iii) I am a member of the MHAUS Professional Advisory Council.

4. In my clinical work and as an MH Hotline Crisis consultant I have encountered and participated in the evaluation and treatment of numerous cases of anesthesia induced MH and the use of Dantrium IV®, some as recently as within the last several weeks.

5. I have published articles and made presentations to clinical and academic professional gatherings on various aspects of the diagnosis of, predisposition to, clinical recognition of, and treatment of anesthesia induced MH crisis. My Curriculum Vitae is attached.

6. I have been informed by Lyotropic Therapeutics, Inc. that that company is developing a low volume, high concentration reformulation of sodium dantrolene, specifically described as follows: an initial effective dose (approximately 100 – 250 mg, depending upon patient weight) will be administrable by a single injection of less than 10 cc, after a single mixing step of lyophilized product with sterile water for injection.

7. I have carefully reviewed the abstracts reporting the research performed by Schütte, Gerbershagen et al, who are among the leading contemporary researchers in the world, entitled "Comparison of Therapeutic Effectiveness of Dantrolene and Ryanodex in Porcine Malignant Hyperthermia" (Anesthesiology 2007; 107: A1922) and "Effects and Safety of the Novel Formulation Ryanodex in Malignant Hyperthermia Normal Swine" (Anesthesiology 2007; 107: A1928) which are attached hereto. The abstracts describe administration of such a low volume, high concentration of dantrolene sodium, supplied by Lyotropic Therapeutics, to both normal and MH susceptible swine, and report comparable efficacy, no adverse effects and significant improvement in ease of dose preparation and administration and decrease in time to prepare and administer an effective dose.

8. I have no further personal knowledge of whether or not this formulation now exists or will in fact be successfully commercially developed as described. However, for the purpose of this Declaration I will assume it to be the case, and use that assumption as the basis for certain of the following comments and opinions.

9. I am not being compensated in any manner by Lyotropic Therapeutics or any other party for preparing this Declaration or in any way related to this proposed new formulation, but rather offer this Declaration because I believe that, should such a formulation actually become available in the clinic, it would mark a significant clinical improvement in the treatment of anesthesia induced MH, one that has been long sought and without success to date.

10. It is broadly accepted by the anesthesia community that the hallmarks for successful management of an MH crisis are timely recognition of the crisis and timely delivery of an effective dosage of dantrolene together with supportive measures. While there are oral formulations of dantrolene on the market, they are of no use in treating MH because the patient is under deep sedation and oral ingestion of any substance would be contraindicated. An injectable formulation must be used, and there are two such formulations available (Dantrium IV®) and a similar generic product.

11. Since its introduction almost 28 years ago, Dantrium IV® has provided tremendous benefit to patients, and together with our growing understanding of the MH crisis and improved monitoring technologies, has saved hundreds of lives in the US and around the world. However, Dantrium IV has significant clinical limitations arising from the sheer bulk of material, and the complex and time-consuming tasks necessary to its preparation and administration as a result of the poor solubility, low concentration and very high volume of the final formulation. In the midst of the MH crisis response, a significant amount of time, attention and personnel is required to locate, retrieve, prepare and administer a therapeutic dose of Dantrium IV. The complexity of the required preparation introduces significant risks of error. For example, there has recently been debate about the temperature of the sterile water used to solubilize Dantrium IV. A significant simplification in the process of preparation and administration of dantrolene or a significant reduction in the time to prepare and administer a full effective therapeutic dose, or ideally both, would constitute a clinically significant improvement in the emergency treatment of an MH crisis for the patient and anesthesiologist. For the reasons

set forth below, this has, since the introduction of Dantrium IV in the 1980s, been a long recognized need of clinicians for such an improved formulation in order to further reduce morbidity and mortality from MH crises.

12. Anesthesia-induced MH is a life threatening, rapidly progressing clinical crisis endangering multiple organ systems and requiring timely and aggressive treatment. Systemic skeletal muscle contractures and increased metabolism in muscle drive the MH crisis cascade, causing elevated CO2, acidosis, cell damage and accumulated metabolic waste products. Administration of a therapeutic amount of dantrolene specifically decreases intracellular calcium in muscle cells thus interrupting skeletal muscle contractures and increased metabolism and so terminating the MH crisis. A formulation that reduces the time required to prepare and complete the administration of a full therapeutic dose of dantrolene to less than five minutes and consequently reduces the time during which patients would be exposed to the cascade of increasingly noxious physiologic events that constitute the MH crisis would unquestionably reduce the risk of morbidity and mortality from MH. For example, within minutes of administration of a therapeutic dose of dantrolene core temperature has decreased 4°C. Reduction of core temperature from 42°C to 38°C in a shorter period of time will reduce the risk of irreversible cerebral damage. (see Bouchama A, Knochel JP. Heat Stroke. N Eng J Med 2002;346:1978-88) In my opinion such a formulation would be a major therapeutic advance in the management of Malignant Hyperthermia. This is a position shared by many clinicians and specialists with whom I am familiar, and has been for many years.

13. In an MH crisis, the risks of morbidity and mortality increase as a function of time and indeed often at an accelerating rate, for several reasons. First, muscle rigidity itself increases the difficulty of successfully treating the crisis, as it diminishes perfusion of the contracting muscle tissue mass and limits the window of time available to effectively deliver Dantrolene to its site of action within the muscle. Second, as a result of acidosis and increasing serum potassium levels, cardiac arrhythmias appear and increase over time, frequently resulting in ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation and pulseless electrical activity (which may result in death). Third,

temperature and acid pH in muscle cells further impair the ability of the cell to control intracellular calcium concentrations. Fourth, rise in body temperature generally presents at late stages of the crisis, and when present temperature may increase at a rate of 1° C per 5 minutes. Therefore any delays in administration of dantrolene directly increase the risk of highly elevated body temperatures. Body temperatures in excess of 104° F are not uncommon in MH cases in which dantrolene administration is not immediate; temperatures in this range generally are associated with cerebral swelling with a potential for brain damage and multiorgan system failure. A reduction in time in the order of 10 to 20 minutes in delivering to the patient the full initial therapeutic dose of dantrolene would in my opinion reduce the risk and incidence of morbidity and mortality.

14. Delays in diagnosis and lack of patient monitoring historically have been factors addressed in improving clinical outcomes, and we now enjoy increased preparedness and improved patient monitoring technology. However, despite these advances, the diagnosis of MH in clinical presentation is often made late in the crisis and consequently the urgency to prepare and administer. The first clinical signs of MH frequently are not specific, and there are many considerations which delay definitive diagnosis. The persistence of this delay underscores the clinical significance of any improvement that reduces the time in which a therapeutic dose of dantrolene can be prepared and administered.

15. Several factors support the proposition that the phenomenon of delayed recognition of MH in the clinic is likely to continue and possibly increase, owing to the spread of the use of anesthesia triggering agents to locations other than dedicated hospital based specialty surgical suites, for example, to ambulatory surgical centers and physician offices. In these new settings, the clinical staff is less likely to be experienced in and trained and prepared for rare complications in the course of anesthesia, and less prepared to diagnose and initiate treatment of MH. In such settings, it is plausible to postulate that the thorough and time consuming process of taking personal history to identify in advance patients with a predisposition to MH is less likely to occur or to be as thorough or as successful in obtaining accurate information, as in major medical centers. In

addition, due to the nature of some of the more common procedures typically performed in these settings, clinicians may be deprived of clinical data which would provide early warning of the MH crisis: such is the case in laparoscopic abdominal procedures where pneumoperitoneum is established and maintained by insufflation of the cavity by introducing carbon dioxide gas under pressure. The high solubility of CO2 results in significant increases in systemic absorption via peritoneal vasculature. This, combined with smaller Tidal Volumes, atelectasis, decreased Functional Residual Capacity and poor lung compliance, leads to markedly increased arterial CO2 levels (hypercarbia). Hypercarbia stimulates the sympathetic nervous system, causing increases in blood pressure, heart rate and arrhythmias. Hypercarbia induced tachycardias and tachyrhythmias are typically treated with short acting beta-blockers, especially in patients with pre-existing cardiovascular disease, to maintain normal rate sinus rhythm. Singly or combined, the existence of hypercapnia and normal sinus rhythm deprive the clinician of the two most commonly recognizable features of the initial signs of an MH crisis; increasing End Tidal CO2 as monitored by capnography and increasing heart rate as monitored by ECG and plethmysography. Furthermore, multiple studies over the years show that a very significant number of the growing number of ambulatory surgical centers and physician offices using triggering anesthetics simply do not have dantrolene on hand. In these circumstances, the only course of treatment involves considerable and unavoidable delay – either a transfer to a dantrolene equipped facility, or retrieval of dantrolene from such a facility.

16. The administration of Dantrium IV is a slow process. For a 70 kg patient, the initial therapeutic dose of 2.5 – 3.0 mg/kg recommended by MHAUS would require administration of over 500 ml of fluid. My experience is that administration of this amount of fluid with standard IV tubing sets requires approximately 20 minutes from the time Dantrium has been reconstituted and readied for administration. Because of this long time and the universal recognition that dantrolene should be administered as rapidly as possible, treatment protocols recommend "pushing" in the formulation if possible. Where this can be accomplished, the time to administration of the full therapeutic dose can be reduced approximately in half, to approximately 10 minutes. However, pushing in

the dose is not possible in all cases, for example, where large capacity veins are not available, for children, for elderly, and in certain procedures such as head and neck surgery. In addition, many patients have had to receive 2 or 3 times more dantrolene, even as much as 10 mg/kg, during initial treatment of MH. Moreover, rapid bolus administration of the dose can cause its own problems. A vein can rupture from pressurized injection, it can spasm and become lumenally occluded, clotting can be induced which can mechanically block the vein as well as create pulmonary emboli: these are not only problematic in their own right, but also may foreclose the established venous access for the administration of dantrolene. If there is an infiltration of Dantrium into extravascular tissues, compartment syndrome can occur due to the mannitol in that formulation. This has been recorded in cases reported to the MH Registry.

17. Within the last several years, together with Dr Marilyn Larach, I reviewed 181 cases voluntarily reported to the North American Malignant Hyperthermia Registry. The results were reported in a subsequent publication (Reassessment of the Safety and Efficacy of Dantrolene; ASA 2002 Annual Meeting, Abstract #6509902), a copy of which is attached hereto. Among our findings were that MH relapse occurred in twenty three percent of the cases. While the average initial dantrolene dose (2.6 mg/kg) was not significantly different between those who relapsed and those who did not, the length of time from the first sign of MH to the initiation of dantrolene administration was significantly greater (63.6 minutes) in patients who experienced a relapse of MH than those who did not (54.1 minutes) ($p<0.001$). As a result, we concluded that initiation of dantrolene treatment in less than 60 minutes after the first sign of MH is noted may be an important therapeutic goal. There is evidence in the MH Registry that delay in administration of dantrolene will result in greater risk of serious complications. This data captures the time to initiation of the therapeutic dose; the time to complete administration of the therapeutic dose is even longer because of the time required to infuse the Dantrium IV. A new formulation that would provide a minimum 20 minute advantage toward that goal would be clinically superior.

18. The following complications were reported among others in the cases we reviewed from the Registry: Hyperkalemia (4%); Renal dysfunction (5.5%); Pulmonary edema (5.5%); Coagulopathy (5.5%); and altered level of consciousness (indicative of cerebral edema) (10%).

19. Cerebral damage incident to MH is caused by prolonged elevation in cranial temperature, with the threshold estimated at 104° F. Body temperature escalation generally occurs later in an MH crisis, but once it appears, can escalate as much as 1° C every five minutes.

20. Long term kidney damage was reported in 4% of the Registry cases. Kidney damage is due to the accumulation in the kidney of myoglobin, a by product of muscle cell breakdown. The amount of kidney damage in my opinion is a function of three factors: how quickly an effective dose of dantrolene was administered, the pH of the urine and the hydration status of the patient.

21. Phlebitis was reported in 10% of the Registry cases. Phlebitis is due to a number of factors in the context of an MH crisis, among which are the need to administer a large volume of Dantrium IV as quickly as possible, the lengthy dwell time at the site of injection (from an infusion of 10 to 20 minute or more), and the tendency to push the large volume injection in order to deliver it more rapidly. In my opinion, delivering the identical dose of dantrolene in a single push of 10 cc or less could be expected to significantly reduce the incidence of phlebitis.

22. The simpler overall protocol for preparing and administering the proposed new dantrolene formulation as compared to Dantrium IV itself represents a significant clinical improvement. Virtually any reduction in the complexity or number of steps or variables or components incumbent upon preparation of Dantrium IV will be reflected in an improvement in patient safety and efficacy, as it reduces the risk of error. In this case, I am assuming that Ryanodex will be prepared on site by withdrawing sterile water for injection from a 10 ml vial. By contrast, Dantrium IV is prepared by mixing multiple

vials with large volumes (one half liter and more) of sterile water for injection. In the surgical suite, it is common to prepare medications with small amounts of sterile water for injection; however, it is rare, if not unique to Dantrium IV, to use very large amounts. Indeed, administration of large volumes of sterile water for injection is contraindicated in most clinical situations. The very presence of one liter bags of sterile water for injection in the surgical suite is cause for a potentially dangerous error and, conversely, the common presence of normal saline or lactated Ringers' lactate in identically sized and shaped one liter bags, is cause for error in the preparation of Dantrium IV. This last point, as well as other preparation errors, is reported by Harrison. (Harrison TK. The use of a cognitive aid for the treatment of malignant hyperthermia. http://www.mhaus.org/index.cfm/fuseaction/Content.Display/PagePK/AbstractTKHarrison.cfm)

23. The well documented and widespread absence of dantrolene from facilities such as ambulatory surgical centers and physician offices in which MH triggering anesthetic agents are administered appears to be the result of a complex set of reasons. One of these is thought to be the unusual, bulky, high volume nature of the formulation. A reformulation that is available in an easier to store use, low volume vial would in my opinion be readily accepted and lead to an increase the availability of dantrolene to additional settings.

24. I am aware of one previous attempt to develop a low volume high concentration formulation of dantrolene sodium in the mid 1990s which failed in in vivo testing and was discontinued. The testing is reported in Anesthesia & Analgesia 1996: 82: 796-802, a copy of which is attached hereto. The article describes in vivo testing of a formulation which can be reconstituted within one minute and with sufficient concentration such that the formulation in a 10 ml vial can contain an initial effective dose, calculated at 2.5 mg/kg. According to the authors, this formulation was being examined for its potential to "eliminate[s] the drawbacks of Dantrium (high pH, Low solubility, cumbersome preparation, and limited access", while meeting Dantrium's profile of safety and efficacy to be an acceptable treatment for MH." The study noted and discussed the adverse

effects of the treatment - pulmonary hypertension, including one case of cardiovascular collapse resulting in death, in swine after administration of [the test formulation]. The study stated "Our data suggest that the pulmonary response to [test formulation] was the result of undissolved dantrolene being release (sic) from [test formulation].... Larger diameter particles appear to be responsible for the pulmonary response, but the exact mechanism is unknown. In theory, filtration should remove the larger particles that can be present as a byproduct of the manufacturing or reconstitution process. However, filtration was not successful in eliminating the pulmonary response of MC-NaD [the test formulation] in swine. Further observations at 200x dilution showed a tendency for MC-NaD [the test formulation] to aggregate even after filtration." I know from personal communications with one of the researchers, a colleague of mine, that development of this formulation was discontinued after publication because of the adverse events, and it has not to my knowledge ever been resumed. The discontinuance of the development of this experimental formulation was at the time a great disappointment to me and other clinicians and specialists in the treatment of malignant hyperthermia, because it meant that the need to overcome the drawbacks of the marketed product still would not be overcome.

25. In my opinion, a formulation of dantrolene for oral administration in no way addresses the long felt need for a low volume, fast acting dantrolene formulation suitable for treating MH. This is because an oral formulation is unsuitable for use in treating MH crisis because the patient is under deep sedation or anesthesia and administration of any drug into the upper GI tract will result in variable absorption and unpredictable plasma concentrations. There has been an acute need for many years for a low volume, high concentration, quickly administered injectable product suitable to administration to a patient in MH crisis, and no product of which I am aware satisfies these needs.

26. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that

such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Barbara W. Brandom, M.D.

Barbara W. Brandom, MD.

February 26, 2008

Date

A1922
October 17, 2007
9:00 AM - 11:00 AM
Room Hall D, Area A,

Comparison of Therapeutic Effectiveness of Dantrolene and Ryanodex in Porcine Malignant Hyperthermia

Mark U. Gerbershagen, M.D., Ph.D., M.B.A., Sandra Becker, M.D., Sascha Burmester, M.D., Alexander Starosse, M.D., Frank Wappler, M.D., Ph.D.
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Introduction: Ryanodex is a novel dantrolene formulation, which is approx. 150 times more water solubile than dantrolene. The aim of this study was to compare the therapeutic management and effectiveness of dantrolene and ryanodex in MH susceptible (MHS) swine.

Methods: Ten MHS swine (age 12±1.1 weeks) were divided in a dantrolene group (n=5, body weight 24.5±3.7 kg) and a ryanodex group (n=5, body weight 24.0±4.0 kg). After premedication, a 22 G catheter was placed in an ear vein and anesthesia was induced with fentanyl and propofol. Following endotracheal intubation controlled ventilation was conducted with an O_2/N_2O mixture (FiO_2=0.45). $PaCO_2$ was set between 38-42 mmHg. Anesthesia was maintained by intravenous administration of fentanyl, propofol and flunitrazepam. Monitoring consisted of ECG, pulseoxymetry, capnometry and invasive measurement of blood pressure. Normothermia was achieved by elevated room temperature. After achieving stable conditions (T_0), MH was triggered by inhalative halothane administration. To avoid a rapid onset MH-crisis, low concentrations of 0.1 (T_1+T_2) and 0.15 (T_3+T_4) Vol% halothane were used for 96 min each. MH-therapy was initiated at pH 7.00±0.05 (T_5). FiO_2 was set to 1.0, respiratory minute volume was doubled and 2 mmol kg^{-1} sodiumbicarbonate administered. To simulate the administration of the substances for a child weighting approx. 24 kg, dantrolene (5 mg kg^{-1}) or ryanodex (5 mg kg^{-1}) respectively were injected via the venous 22 G cannula. Time needed for establishing an aqueous solution and time needed for injection was measured. After MH-therapy data were monitored every 24 min (T_6+T_7). Data are shown as mean and standard deviation (t-test, $p<0.05$).

Results: Course of MH-crises and therapeutic effects were comparable between the groups.[table1]Normalisation of heart rate, blood pressure and lactate were similar (data not shown). Time needed for establishing an aqueous solution was significantly shorter for 5 mg kg^{-1} ryanodex (50.6±8.5 sec) compared to dantrolene (860.3±201.8 sec). Likewise injection time of ryanodex (4.2±1.7 sec) was significantly shorter than of dantrolene (471.5±50.5 sec).

Conclusion: Therapeutic action of ryanodex is comparable to dantrolene. Yet, preparation and administration of the ryanodex solution was faster. Therefore, ryanodex seems to be a promising agent in treatment of MH.

This study was partly supported by the German Research Foundation and by BBraun.

Anesthesiology 2007; 107: A1922

Table 1: Course of pH, pCO_2 and temperature during halothane administration and adjacent therapy

	artierial pH		arterial pCO_2		temperature	
time	dantrolene	ryanodex	dantrolene	ryanodex	dantrolene	ryanodex
T_0	7.46±0.03	7.46±0.05	40.0±1.0	40.8±1.8	38.6±0.4	38.5±0.8
T_1	7.40±0.06	7.45±0.06	44.6±6.1	43.6±2.4	38.6±0.5	38.6±0.6
T_2	7.37±0.09	7.40±0.07	47.8±8.3	47.8±5.8	38.6±0.5	38.6±0.7
T_3	7.32±0.10	7.36±0.01	52.2±10.4	51.4±8.6	38.8±0.6	38.9±1.0
T_4	7.20±0.13	7.20±0.08	65.2±16.2	69.2±9.2	39.1±0.6	39.5±1.6

T_5	6.97±0.05	7.04±0.07	111.0±7.4	101.5±5.6	40.4±0.9	40.1±0.9
T_6	7.39±0.16	7.43±0.17	45.6±7.3	47.0±10.8	40.1±0.8	40.2±0.5
T_7	7.43±0.04	7.47±0.07	46.4±3.8	44.8±2.6	39.8±0.8	39.9±0.8

A1928
October 17, 2007
9:00 AM - 11:00 AM
Room Hall D, Area A,

Effects and Safety of the Novel Formulation Ryanodex in Malignant Hyperthermia Normal Swine

Jan K. Schütte, M.D., Mark U. Gerbershagen, M.D., Ph.D., M.B.A., Christiane Hötzel, M.D., Martin Larisch, M.D., Frank Wappler, M.D., Ph.D.
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Introduction: Ryanodex is a novel hydrophilic dantrolene formulation, which is 150 times more water solubile than dantrolene. The aim of this study was to assess the safety of ryanodex in malignant hyperthermia normal (MHN) swine.

Methods: Seven MHN swine were examined in this study. After premedication with ketamine intramuscularly, a 22 G catheter was placed in an ear vein and anesthesia was induced with fentanyl and propofol. Following endotracheal intubation, controlled ventilation was conducted with an O_2/N_2O mixture (FiO_2=0.45). $PaCO_2$ was set between 38-42 mmHg. Anesthesia was maintained by continuous intravenous administration of fentanyl (50 µg $kg^{-1}h^{-1}$), propofol (4 mg kg^{-1} h^{-1}) and flunitrazepam (0.1 mg kg^{-1} h^{-1}). ECG, pulseoxymetric and intramuscular temperature monitoring were conducted. Two arterial catheters, one for blood gas analyses and one for pulse contour analyses, were inserted. Additionally, a central venous catheter was placed. Normothermia (100.4-101.8 Fahrenheit) was achieved by elevated room temperature. After achieving steady state conditions (T_0), inhalative halothane administration was applied in concentrations of 0.1 (96 min, T_1), 0.15 (96 min, T_2) and 0.2 Vol% (48 min, T_3). Thereafter, halothane administration was stopped and 5 mg kg^{-1} ryanodex was administered intravenously (T_4). Bolus injection of 5 mg kg^{-1} ryanodex was repeated after 24 min (T_5). Parameters were monitored after another 24 and 48 min (T_6+T_7). Data are shown as mean and standard deviation. Changes in test series were analysed with the t-test. * $p \leq 0.01$

Results: Laboratory parameters were not affected by the administration of ryanodex (arterial pH, pCO_2, HCO_3, potassium and lactate).[table1]Alike, no differences in hemodynamic parameters were monitored, either (heart rate, systolic-, diastolic-, mean arterial blood pressure, cardiac index). Temperature was also unaltered. Other potential side effects, such as sweating and shivering, were not observed.

Conclusion: Administration of ryanodex did not alter laboratory and hemodynamic parameters. The intravenous administration of ryanodex seems to be safe in swine. Therefore, it is worthy to examine the effectiveness of that substance in the treatment of MH crisis in MH susceptible swine.

This study was partly supported by the German Research Foundation and by BBraun.

Anesthesiology 2007; 107: A1928

Table 1: Course of hemodynamic and laboratory parameters during halothane administration and adjacent ryanodex therapy

time	test protocol	arterial pH	arterial pCO_2	temperature	blood lactate	cardiac index
T_0	steady state	7.46±0.03	39.0±1.4	38.8±1.6	1.3±1.5	3.46±0.44
T_1	0.1 Vol% halothane	7.47±0.02	39.3±2.1	38.6±1.6	1.5±1.1	3.49±0.56
T_2	0.15 Vol% halothane	7.46±0.03	39.9±2.2	38.5±1.2	1.0±0.5	3.53±0.61
T_3	0.2 Vol%	7.42±0.04	42.7±4.5	38.4±1.2	0.9±0.3	3.47±0.86

	halothane					
T_4	5mg kg^{-1} ryanodex	7.42±0.05	43.4±3.8	38.6±1.2	0.8±0.3	3.25±0.53
T_5	5mg kg^{-1} ryanodex	7.41±0.05	42.5±5.6	38.3±0.9	0.9±0.2	2.95±0.54
T_6		7.39±0.04	44.1±6.3	38.3±1.1	1.1±0.3	2.86±0.25
T_7		7.40±0.06	44.3±5.7	38.3±1.1	0.9±0.3	2.91±0.34

A-1199
2002

Reassessment of the Safety and Efficacy of Dantrolene

Barbara W. Brandom, M.D.; Marilyn G. Larach, M.D.; The North American Malignant Hyperthermia Registry.
Anesthesiology, University of Pittsburgh, Pittsburgh, Pennsylvania

INTRODUCTION: In the North American Malignant Hyperthermia Registry (NAMHR) 99 of 461 Adverse Metabolic/Musculoskeletal Reaction to Anesthesia (AMRA) reports describe MH episodes prior to 1993. The effects of dantrolene in this group were reported in abstract in 1993[1].Three patients died. We reviewed the NAMHR to see if results have changed since.

METHODS: Case inclusion criteria were: date of anesthesia after January 1, 1993 and before February 2002, Clinical Grading Score[2] [>]34 (CGS), indicating very likely or almost certain MH, documentation of weight and either initial or total dose of dantrolene. 181 AMRAs met these criteria.

RESULTS: More males than females ($p< 0.0001$), 78% versus 21%, were reported. All survived the acute episode and 42 episodes of relapse. Dantrolene was not given to 17 of these patients. MH relapse occurred in 23%. The mean CGS, 58 versus 53, and total dose of dantrolene, 9.6 (sem 0.4) versus 7.8 (sem 0.3) mg/kg were significantly greater in those with relapse (p[<]0.01).The mean time of relapse was 6.5 (sem 0.4) hours after the first dose of dantrolene. Causes of delayed death included hyperkalemia and acute renal failure (1), cerebrovascular insufficiency (2) and AIDS with sepsis (1). These 4 patients had not suffered relapse of MH. The mean initial dantrolene dose was 2.6 mg/kg (sem 0.11), not significantly different with relapse. The largest initial dose was 10.3 mg/kg. The largest total dose was 29 mg/kg. In the 164 cases that received dantrolene the most frequent complications were muscle weakness in 22% (36) and phlebitis in 10% (11). All other acute complications occurred in less than 5%. Respiratory failure and gastrointestinal upset were noted in only 3% (5 each). Excessive secretions were noted in < 1% (1). Complications that could be related to the course of MH or other underlying disease were present in < 10% of cases. These included hyperkalemia in 4% of patients (7), renal dysfunction, edema or coagulopathy in 5.5% (10 each). In 9 of the 10 cases of renal failure dantrolene was given. In those cases where no renal failure was noted 16 did not receive dantrolene and 155 did. Thus there was no difference in risk of renal failure as a function of dantrolene treatment ($p=0.62$). To detect a reduction in risk of renal failure from 5% to 2.5% with power of 0.8, over 900 patients in each treatment group would have to be observed.

DISCUSSION: This review suggests that an initial dose of 2.5 mg/kg dantrolene followed by 1 mg/kg every six hours for [>] 24 hours is useful for most patients. Perhaps decreasing the interval between repeat doses to 4 hours would reduce the number of relapses. Although we report no fatalities due to uncontrolled MH in this study of recently treated patients, we continue to note the same incidence of relapse and complications as that reported in 1993. Muscle weakness and phlebitis continue to be frequent complications.

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1. Anesthesiology 79:A1079, 1993.

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Anesthesiology 2002; 96: A1199

Use of Cognitive Aids in a Simulated Anesthetic Crisis

T. Kyle Harrison, MD
Tanja Manser, PhD
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We evaluated empirically the extent to which the use of a cognitive aid during a high-fidelity simulation of a malignant hyperthermia (MH) event facilitated the correct and prompt treatment of MH. We reviewed the management of 48 simulated adult MH scenarios; 24 involving CA 1 and 24 involving CA 2 residents. In the CA 1 group, 19 of the 24 teams (79%) used a cognitive aid, but only 8 of the 19 teams used it frequently or extensively. In the CA 2 group, 18 of the 23 teams (78%) used a cognitive aid but only 6 of them used it frequently or extensively. The frequency of cognitive aid use correlated significantly with the MH treatment score for the CA 1 group (Spearman $r = 0.59$, $P < 0.01$) and CA 2 group (Spearman $r = 0.68$, $P < 0.001$). The teams that performed the best in treating MH used a cognitive aid extensively throughout the simulation. Although the effect was less pronounced in the more experienced CA 2 cohort, there was still a strong correlation between performance and cognitive aid use. We were able to show a strong correlation between the use of a cognitive aid and the correct treatment of MH.
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Malignant hyperthermia (MH) is a rare genetic disorder of metabolism that, when triggered by drugs used in anesthesia, creates a major crisis. The incidence of MH ranges from 1 in 62,000 to 1 in 84,000 for general anesthetics in which succinylcholine and inhaled anesthetics are used (1). With this incidence, most anesthesia professionals will never treat a case of MH during their career. Once the diagnosis of MH has been made, a complex and specific treatment plan needs to be implemented quickly and efficiently to prevent a fatal outcome. A treatment scheme has been produced by the Malignant Hyperthermia Society of the United States (MHAUS; www.mhaus.org) to guide practitioners in the treatment of MH.

As a general rule, medicine has relied heavily on clinicians' recall of information as the primary basis for treatment decisions even in emergent settings. Relying on memory may work well when the situation is familiar and there is little stress, but during a stressful situation, memory is likely to be error-prone, resulting in omissions or treatment missteps (2). Acute stress can also have a negative effect on other cognitive functions with a decrease in both selective and divided attention (3).

Written or computerized presentation of important information can be referred to generically as "cognitive aids." Cognitive aids are not just for novices, nor are they simply "learning aids." Rather, they provide prompts for and reviews of important diagnostic or corrective actions that can be used during case management by all levels of personnel. A few written cognitive aids are available for routine and emergency procedures in health care. In 1993, the United States Food and Drug Administration developed a pre-use anesthesia apparatus checkout recommendation (4). Despite the importance of the anesthesia machine check, the Food and Drug Administration's checklist has been found to be poorly understood and difficult to use (5,6). Recently, a checklist was found to be useful before general anesthesia for simulated Cesarean delivery (7). Advanced Cardiac Life Support treatment guidelines have been available for a number of years, but their use is variable and the full Advanced Cardiac Life Support algorithms are difficult to navigate during a crisis (8,9). Despite these and other examples, the use of cognitive aids in routine or emergent patient care settings is not common in health care (10), in contrast to other high-risk industries such as aviation and nuclear power.

We hypothesized that cognitive aids would be useful in the treatment of a rare event like MH. We empirically evaluated the extent to which the use of cognitive aids during a simulated MH event facilitated correct and prompt treatment of the event.

METHODS

We reviewed audiovisual recordings of 48 scenarios of simulated MH; 24 involving residents in their first Clinical Anesthesia year (CA 1) and 24

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Table 1. Malignant Hyperthermia (MH) Treatment Score

Treatment	Points	Treatment	Points
Anesthetic gas off	3	Appropriate dose dantrolene	1
High flow oxygen	3	First dose 20 mg ≤ 10 min	3
Cooling	3	First dose 20 mg ≤ 15 min	2
Surgeon notified	1	First dose 20 mg ≤ 20 min	1
Treatment of hyperkalemia	1	Second dose 20 mg ≤ 15 min	3
Administer $NaHCO_3$	1	Second dose 20 mg ≤ 20 min	2
Labs sent	1	Second dose 20 mg ≤ 30 min	1
Mixed dantrolene 60 cc/H_2O	3	Third dose 20 mg ≤ 30 min	2
		Maximum Score (both columns)	25

Determination of the MH treatment score.

involving CA 2 residents. All subjects gave informed consent to participate in this IRB-approved study.

The simulation scenarios were part of the Anesthesia Crisis Resource Management (ACRM) course conducted at Stanford/Veterans Administration Health Care System Palo Alto from 1998–2003 (11,12). The simulations were performed in a simulation center using a high capability patient simulator (MedSim Eagle, Sarasota, FL). During the scenarios an experienced anesthesiologist instructor played the surgeon's role. The circulating nurse was played by a retired operating room nurse, and the "scrub tech" was played by one of the participants. In the scenario, anesthetic care was handed off to the primary participant by a confederate anesthesiologist after induction of anesthesia was complete. Another course participant of equal level of training was sequestered in a sound-proof room and could be summoned for help by the primary anesthesiologist if requested.

The case scenario for the CA 1 participants involved a general anesthetic on a healthy adult female undergoing a knee operation. Succinylcholine had been used and anesthesia was maintained with isoflurane and nitrous oxide. The case scenario for the CA 2 participants was more complex and involved a laparoscopic appendectomy on a female patient with a history of Graves' disease. In this case, succinylcholine and isoflurane were also used. For both scenarios, the patient became progressively unstable over 15–20 min with signs of hypermetabolism (increasing heart rate, arterial blood pressure, temperature, and increased production of carbon dioxide) and hyperkalemia (peaked T waves and increasingly frequent premature ventricular contractions). Although participants had to diagnose the presence of MH, in this experiment we studied only the treatment of MH but not the timing or pathway to the diagnosis. Performance was scored only from the point when the participant(s) articulated a diagnosis of MH.

Subjects were instructed to bring to the simulated operating room any materials that they routinely carried into a regular day of work, including any books or personal data assistants. If participants requested the MH cart, they were brought a large box containing all critical items needed to treat MH. Easily accessible in the MH box (placed on top of the other supplies) was the MHAUS poster detailing appropriate treatment of MH. We did not provide formal training concerning the treatment of MH, the contents of the MH box, or the use of cognitive aids before the simulation.

We developed a scoring system to assess the clinical performance of the team, based on a system we described in a previous publication (13) and similar to scoring systems used by other investigators (14) (15). Points were assigned for the various treatment steps needed to successfully treat an episode of MH as outlined by MHAUS (Table 1). The videotaped scenarios were analyzed by two of the authors (TM and KH). For each treatment step, we recorded the time from articulating the diagnosis of MH (time 0) until successful completion of that step by any member of the team. A MH treatment score was calculated from the point values of steps accomplished.

We attributed an action to the use of a cognitive aid if a) an individual's action immediately followed reading a cognitive aid or b) any member of the team stated that the action was in response to an item on a cognitive aid. In addition to the MH treatment score, the overall frequency of cognitive aid use was scored independently by the authors (TM and KH) using a 5-point scale with 0 = no use, 1 = minimal use, 2 = occasional use, 3 = intermittent use, 4 = frequent use, and 5 = extensive use. Extensive use required the participants to use an aid throughout the entire treatment of the MH crisis.

Aggregate data are shown as mean ± SD unless otherwise specified. MH treatment scores and ratings for frequency of cognitive aid use were correlated separately for the CA 1 and the CA 2 group using nonparametric (Spearman) correlation (because the frequency scale was ordinal). In addition we calculated for each treatment step the percentage of CA 1 and CA 2 teams that had used a cognitive aid. Both observers rated the frequency of cognitive aid use independently. A Cohen's kappa of 0.94 for their ratings of the same teams indicates excellent interobserver agreement (16,17).

RESULTS

In every scenario the primary anesthesiologist requested and received assistance from the sequestered

anesthesiologist. All teams of anesthesiologists made the diagnosis of MH except for one set of CA 2 participants who attributed all symptoms to hyperthyroidism. Because the scoring system is based on the time from articulation of the diagnosis of MH to the occurrence of treatment steps, we excluded this case from the analysis. The average time from triggering the MH event on the simulator to the participants declaring an MH emergency was 19 (±4.5) min for the CA 1 group and 26 (±9.4) min for the CA 2 group (likely related to the confounding variable of Graves' disease and the possibility of thyroid storm). The average treatment score for the CA 1 group was 19.8 (±3.9) and for the CA 2 Group it was 21.4 (±3.3).

The most frequently used cognitive aid was the MHAUS poster that was provided in the MH box. Some teams used an alternative aid, such as a textbook or personal digital assistant reference, but none of the teams used an alterative aid frequently or extensively. Of the top scoring teams that used an aid, all used the MHAUS poster. In the CA 1 group, 12 teams used the poster and 7 teams used an alternative aid. In the CA 2 group, 16 teams used the MHAUS poster and 2 teams used an alternative aid. In the CA 1 group, 19 of the 24 teams (79%) used some form of a cognitive aid, but only 8 of the 19 teams used it frequently or extensively. In the CA 2 group, 18 of the 23 teams (78%) used some form of a cognitive aid at some point, but only 6 of them used it frequently or extensively. The frequency of cognitive aid use correlated significantly with the MH treatment score for the CA 1 group (Spearman $r = 0.59$, $P < 0.01$) as well as for the CA 2 group (Spearman $r = 0.68$, $P < 0.001$).

In the CA 1 group, the 5 highest scoring teams (average MH treatment score of 24.2) had a mean score for cognitive aid use frequency of 4.2 and the 5 lowest scoring teams (average treatment score of 14.4) had a mean frequency of use score of 1. In the CA 2 group, the 5 highest scoring teams (average MH treatment score of 24.4) had a cognitive aid use frequency score of 4.4 and the 5 lowest scoring teams (treatment score of 16.8) and a frequency of use score of 0.4 (Fig. 1).

As summarized in Table 2, 41 teams determined the correct dose of dantrolene, with 26 teams (55%) using a cognitive aid to determine that dose (23 teams using the MHAUS poster and 3 teams using an alternative aid). The average time from diagnosis until the injection of the first dose of dantrolene was 7.2 (±3.8) min for the CA 1 group and 6.5 (±3.2) min for the CA 2. Only 10 of 24 teams (42%) mixed the dantrolene correctly in the CA 1 group and 18 of 23 (78%) mixed the dantrolene correctly in the CA 2 group. Of the teams that mixed the dantrolene correctly, 70% used a cognitive aid in the CA 1 group and 72% did in the CA 2 group. For the CA 1 teams that mixed the dantrolene incorrectly, 8 used both the wrong volume and the wrong diluent (typically lactated Ringer's solution instead of sterile water). Five teams used the wrong diluent but the correct volume, and one team used the wrong volume but correct diluent. Of the 5 CA 2 teams that mixed the dantrolene incorrectly, 3 teams used the wrong volume, 1 team the wrong diluent, and 1 team both. Of the 19 teams that mixed the dantrolene incorrectly, only 1 team used a cognitive aid.

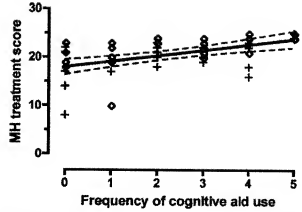

Figure 1. Relationship of frequency of cognitive aid use and malignant hyperthermia (MH) treatment score for CA 1 (+) and CA 2 (◇) teams. Regression line (Spearman $r = 0.54$) and 95% confidence interval lines are shown. Frequency use: 0 = no use; 1 = minimal use; 2 = occasional use; 3 = intermittent use; 4 = frequent use; 5 = extensive use.

The treatment step that was most often associated with the use of a cognitive aid was determining the correct dose of dantrolene, with 41% of the CA 1s using a cognitive aid and 69% of CA 2s using an aid. The most frequently missed treatment step was treating hyperkalemia (typically >6.0 mEq/L), which was also manifested by peaked T-waves and frequent premature ventricular contractions. More than half of teams (58% of CA 1s and 69% of CA 2s) failed to treat hyperkalemia.

DISCUSSION

A simulated MH event is an excellent model to test how anesthesia providers respond to a rare but potentially lethal condition. With the widely accepted and defined treatment protocol for MH, we were able to assess how the use of a cognitive aid affected overall performance. We assumed that every duo of anesthesia providers should be able to achieve a perfect score for the MH treatment and that any deficiency could represent a significant problem with the care delivered.

In this study, the average MH treatment score for all participants was 20 (of 25) but ranged from 8 to 25, with most provider teams failing to accomplish at least one major treatment step. We found a statistically significant association between frequency of cognitive aid use and MH treatment performance. The teams that performed the best, as measured by treatment score, used a cognitive aid extensively throughout the simulation and the teams that performed worst failed to use any form of a cognitive aid (Fig. 1). However, use of the cognitive aid explained only 1/3 to 2/3 of

Table 2. Treatment Steps Attributed to Cognitive Aid Use

	CA 1 (n = 24)			CA 2 (n = 23)		
	No	Yes		No	Yes	
Treatment step		No Cog. Aid	Cog. Aid		No Cog. Aid	Cog. Aid
Appropriate dose dantrolene	8.3	50.0	41.7	—	30.4	69.6
Mixed dantrolene 60 cc/H_2O	58.3	12.5	29.2	—	39.1	60.9
Anesthetic gas off	—	95.8	4.2	—	91.3	8.7
High flow oxygen	12.5	75.0	12.5	30.4	39.1	30.4
Cooling	4.2	75.0	20.8	13.0	69.7	17.4
Surgeon notified	—	100	—	—	100	—
Administer $NaHCO_3$	37.5	20.8	41.7	26.1	47.8	26.1
Treatment of hyperkalemia	58.3	20.8	20.8	65.2	17.4	17.4
Labs sent	29.2	41.7	29.2	56.5	39.1	4.3

The number of participants that completed a treatment step and if the treatment step was attributed to a cognitive aid (expressed as %).

the variance in treatment score. There were probably many other factors that affected the adequacy of treatment, including adequacy of teamwork and skill in executing the actions recommended by the cognitive aid.

We observed several "patterns" of cognitive aid use, suggesting that it is not only how frequently an aid is used but also how an aid is integrated in the process of managing an anesthetic crisis that determines performance. Some teams used a cognitive aid early in the MH event and continued to cross-check it throughout the scenario. Several teams read the instructions out loud and other team members responded; this helped establish shared situational awareness. Teams using these two strategies were the highest performing in the study. Other teams did not use a cognitive aid at all or used it only late in the scenario. Some teams that used an aid late often did pick up previously forgotten steps, such as treating hyperkalemia and acidosis. Some individuals consulted an aid but failed to share the information with other team members, resulting in a delay in appropriate management.

Observing participants' use of the MHAUS cognitive aid, it was apparent that the existing cognitive aid failed to clarify relative priorities. In particular, the need to expedite delivery of dantrolene as the highest priority is not transmitted optimally in this cognitive aid. Although the CA 2 teams were faster at administering the first and additional doses of dantrolene as compared to the CA 1 group (Table 3), some teams spent considerable resources on lower priority actions (e.g., attempting to replace the anesthetic machine, placing a nasogastric tube for topical cooling) and thereby delayed administering an appropriate dose of dantrolene. Also, many participants hyperventilated the lungs by hand, occupying one member of the team on a task that could have easily been accomplished by mechanical ventilation. i Gardi et al. (14) also observed this behavior in their study of performance managing simulated MH. Optimal cognitive aids should anticipate common errors and provide prioritized and explicit instructions to prevent them.

A surprising finding of this study was that so many of the anesthesia teams failed to mix the dantrolene correctly. Despite the label on the bottle of dantrolene stating how to properly mix the drug, and the same directions also being printed on the MHAUS treatment poster, 45% of the teams still mixed the drug incorrectly.

The time to diagnosis was longer for the CA 2 than the CA 1 group. In the CA 2 case there were three major confounding factors that might have caused the delay in diagnosis. First, the patient had a history of Graves' disease and it was plausible (at first) that the patient was experiencing "thyroid storm." In addition, the patient was undergoing laparoscopic surgery for appendicitis and thus the patient's increased CO_2 could have been related to insufflation of CO_2, and the patient's fever and hyperdynamic hemodynamic state might have resulted from sepsis. In addition, the CA-2 participants in ACRM2 had seen a case of MH in the ACRM1 course the previous year and thus they might

Table 3. Dantrolene Dosing

Administration of Dantrolene	% of Teams
CA 1 (n = 24)	
1st dose 20 mg ≤ 10 min	87.5
1st dose 20 mg ≤ 15 min	4.2
1st dose 20 mg ≤ 20 min	4.2
1st dose not given	4.2
2nd dose 20 mg ≤ 15 min	79.2
2nd dose 20 mg ≤ 20 min	8.3
2nd dose 20 mg ≤ 30 min	4.2
2nd dose not given	8.3
3rd dose 20 mg ≤ 30 min	50.0
3rd dose not given	50.0
CA 2 (n = 23)	
1st dose 20 mg ≤ 10 min	95.7
1st dose 20 mg ≤ 5 min	4.3
1st dose 20 mg ≤ 20 min	—
1st dose not given	—
2nd dose 20 mg ≤ 15 min	95.7
2nd dose 20 mg ≤ 20 min	4.3
2nd dose 20 mg ≤ 30 min	—
2nd dose not given	—
3rd dose 20 mg ≤ 30 min	65.2
3rd dose not given	34.8

have inferred that a repeat MH case was unlikely. From post-scenario think-aloud debriefing, (although we did not formally measure this), it appears that the confounding diagnosis of Graves' disease was by far the most likely cause for the delay in diagnosis. Although a cognitive aid might help some individuals to make the diagnosis of MH in the face of such uncertainty, this was not evaluated in this study. We evaluated the use of a cognitive aid only from the time the diagnosis was made.

This study has a number of limitations. First, we do not know the effect on patient outcome from failing to complete some of the treatment steps outlined in the MHAUS treatment protocol or of executing them incorrectly. It seems likely that major deviations from the protocol would lead to suboptimal outcomes or to greater liability exposure. Another limitation is that the study was retrospective, using scenarios that were designed for teaching rather than for the primary purpose of investigation. The scenarios somewhat compress time relative to the probable time course of MH in real patients; thus, it is not certain that failures or errors seen during simulations would always occur in real patient care. Because of the retrospective character of this study, it was not possible to obtain systematic interview data from the participants regarding their use of the cognitive aid or their reasons for not using an aid. This means that we cannot determine how often a cognitive aid provided information that the team did not already posses, versus reminding them about or confirming their prior knowledge. Further, during a real MH emergency during normal working hours, more personnel might be available to provide their knowledge and physical help. In addition, the participants were anesthesia residents and not fully trained anesthesia professionals. However, in the study by i Gardi et al. (14) looking at the management of MH in experienced teams consisting of nurse-anesthetists (average 8.3 years experience) and anesthesiologists (average 9.8 years experience), only half of the teams administered sodium bicarbonate and only a third administered insulin and glucose for hyperkalemia, findings similar to our own observations of residents.

An additional limitation of this is study is that we cannot know the amount of prior knowledge the participants had in the diagnosis and treatment of MH. The residents received one formal lecture on drug-induced hypermetabolic disorders (including MH) in their residency lecture series. During the ACRM2 course, we scheduled scenarios such that the CA 2 participants who participated in the "hard" MH scenario would not have been either the primary anesthesiologist or first responder anesthesiologist in the "easy" MH scenario that was run during the ACRM1 course in their CA1 year. However, those CA2 residents would have witnessed and participated in the group debriefing of the MH scenario during ACRM1. If they remembered their ACRM1 experience it might have assisted them in managing MH in the ACRM2 course over 1 year later.

Recently, the Veterans Health Care Administration (VHA), in conjunction with the VHA National Center for Patient Safety, has produced a series of cognitive aids for crisis events in anesthesia. These aids are now placed on all anesthesia machines in the VHA system. In a follow-up survey of VHA anesthesia providers, they found that 87% of the respondents had seen the aid and half had used it as a reference but that only 7% had used it in an emergency. However, of the small number of providers who had used it in an emergency, all felt that it had helped (personal communication, J. Neily et al. VA National Center for Patient Safety, 2005).

Hart and Owen (7) have recently shown anesthesia providers on average omitted 13 of 40 steps when preparing to administer general anesthesia for cesarean delivery. When provided with a checklist, 90% of the participants found the checklist useful but only 40% stated that they would use it clinically. Morris (10) has shown that there are several barriers to physicians using guidelines and protocols. These include a lack of appreciation of the limitations of human decision-making, excessive complexity in the protocols, and the concern that the use of protocols could reduce the role for clinicians in medicine. In addition, in a critical time-sensitive event the use of an aid might be perceived as an additional burden, despite its potential benefits.

The use of cognitive aids in medicine differs from other industries such as aviation and nuclear power in many ways. The latter are highly regulated both by the employer and the government, and personnel in these industries are mandated to use checklist-type cognitive aids to provide a more consistent response in standard operating procedures. Medicine involves a much more complex and unpredictable system. A simple checklist may not be adequate to cover the complex environment in health care. However, for many unusual but acute conditions in medicine, a cognitive aid is likely to be helpful in providing additional therapeutic and diagnostic guidance to clinicians. A computerized system of cognitive aids, On-Line Electronic Help, designed for use at the point-of-care for routine and emergent anesthetic situations, has recently been developed by Berkenstadt et al. (18) and endorsed by the European Society of Anesthesiologists. The On-Line Electronic Help system has been shown to improve clinicians' performance for various scenarios on a "screen-based" anesthesia simulation (18).

Although we recommend that health care providers be encouraged to use cognitive aids, we also believe that the design of such aids should be improved. Although the pertinent information for the treatment of MH was provided on the MHAUS poster, the key information did not appear to be transmitted to the participants in all cases. Swain and Guttman

(19) found that in nuclear power operations, as the number of items on a checklist increased, there was a greater probability of overlooking a given item. In addition, if a step could not be completed immediately when read on a checklist, the user would often try to store the step in their short-term memory, which is prone to failure under stressful conditions, resulting in omissions (20). Attempts to improve the MHAUS treatment poster could include breaking the various steps into discrete sections or separate aids (diagnosis, treatment, follow-up care) so that there are fewer steps in any one section. The most critical items should be listed first to increase the probability that they will not be missed or omitted. In addition, critically important steps might be repeated throughout the aid to reinforce their impact. For example, information on how to properly mix dantrolene or how to treat hyperkalemia could be duplicated in different places, and with a size and font that would make them stand out. Our findings support that conception and design of cognitive aids is an area for further research especially if they are to be effectively used in health care.

In other high-risk professions, such as aviation or spaceflight, checklists and other cognitive aids are used as part of standard operating procedures. Negative stereotypes about the use of cognitive aids in health care should be confronted. Although we did not question the participants directly about why they did not use a cognitive aid in this study, in informal discussions with residents, many felt that using a cognitive aid would tend to show weakness and give the impression that they did not know what to do in a crisis. In this study, not all of the teams needed a cognitive aid to perform well, but the teams that performed well often did use an aid, and the teams that performed the worst did not use any form of an aid. Because it is impossible to determine prospectively if a team will perform well in a crisis, it might be prudent to encourage all teams to refer to and use a cognitive aid in unfamiliar or life-critical situations to maximize the likelihood of successful resolution.

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Intravenous Lecithin-Coated Microcrystals of Dantrolene Are Effective in the Treatment of Malignant Hyperthermia: An Investigation in Rats, Dogs, and Swine

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Dantrolene effectively treats malignant hyperthermia (MH) but the current form, Dantrium®, must be dissolved to a 0.33 mg/mL, pH 9.5 solution. This study describes lecithin-coated microcrystal formulations of sodium dantrolene (MC-NaD) and neutral dantrolene (MC-D) which reconstitute to 200 mg/mL within 1 min. In rats, the pharmacokinetics and pharmacodynamics of MC-NaD and Dantrium® were similar: half-lives of 3.1 h, volume of distributions of 0.54 and 0.59 L/kg, and 95% effective dose (ED_{95}) values for depression of skeletal muscle twitch height ($ED_{95}T$) of 2.6 ± 0.7 and 2.8 ± 0.5 mg/kg. In swine, the $ED_{95}T$ values for MC-NaD and Dantrium® were also similar (2.8 ± 0.4 vs 2.7 ± 0.6 mg/kg), but MC-D and Dantrium® were only similar at doses more than 2.5 mg/kg ($ED_{95}T$: 3.5 ± 0.4 vs 2.7 ± 0.5 mg/kg). In susceptible swine, MC-NaD successfully treated five of six MH episodes and prevented MH in three of four swine. However, MC-NaD caused marked pulmonary hypertension in swine, while MC-D caused only a mild response that was eliminated by filtration. Likewise, MC-D caused no pulmonary response in dogs. These observations suggest that MC-D has potential to improve the treatment of MH.

(Anesth Analg 1996;82:796–802)

Dantrolene has been the cornerstone of treatment for malignant hyperthermia (MH) for over 15 y. The currently available form of dantrolene sodium for the treatment of MH is Dantrium® Intravenous (Procter & Gamble, Cincinnati, OH), a lyophilized formulation in units of 20 mg which are reconstituted with sterile water (60 mL) to produce a 0.33 mg/mL, pH 9.5 solution. The present study reports delivery forms which can be more rapidly reconstituted and administered. Lecithin-coated microcrystal technology (1) was applied to dantrolene to make lyophilized preparations which can be reconstituted with sterile water within one minute to produce stable, intravenously (IV) injectable suspensions of submicron dimension: lecithin-coated microcrystals of sodium dantrolene (MC-NaD) and neutral dantrolene (MC-D). Injected concentrations can be as large as 200 mg/mL. A 10-mL vial can contain enough dantrolene to initially treat an 80-kg adult (2.5 mg/kg) and could easily be stocked at any anesthetizing location.

The present study compares the lecithin-coated microcrystal formulations (MC-NaD and MC-D) with the commercial Dantrium® solution (D) in rats, dogs, and normal swine. Nelson and Flewellen used the depression of muscular twitch height in swine (2,3) and humans (4) to determine the dose for dantrolene therapy in the treatment of MH. These values provide the guidelines for the current dantrolene treatment recommendations. Our experiments were modeled after their work to evaluate safety (response to small, incremental dosing), efficacy (twitch height depression), and validation of results. In addition, we have compared MC-NaD and D for the prophylaxis and treatment of MH in MH-susceptible (MHS) swine.

Methods

The animal care and procedures used in this study were approved and performed in accordance with the

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animal care and use committee of the Uniformed Services University of the Health Sciences.

Preparation of Lecithin-Coated Microcrystals of Dantrolene

To produce MC-NaD, 20 mg of Pfanstiehl P123 egg phospholipids (Lot 21097) and 20 mg dantrolene sodium (Procter & Gamble Pharmaceuticals, CN:62699, RX31551) suspended in 300 mM glucose and 2 mM sodium phosphate buffer at pH 8.2 to a final volume of 200 mL were homogenized and passed seven times through an M-110F Microfluidizer® (Microfluidics Corp., Newton, MA) at 12,000–14,000 psi. The MC-NaD suspension had an average particle size of less than 1 μ. Samples were lyophilized in 10-mL serum vials, and were submitted for testing. After reconstitution with distilled water at 10%–15% (wt/vol dantrolene), a stable suspension was obtained immediately. Microscopic observation revealed 300–800 nm free-flowing particles.

MC-D were prepared in an identical fashion, except that (a) dantrolene sodium was first reacted with hydrochloric acid to prepare the neutral species and (b) the pH was 5.3. The lyophilized MC-D product also suspended rapidly upon the addition of distilled water to give a stable suspension of 500–800 nm free-flowing particles. Coulter N4MD laser particle size analysis gave 440 ± 150 nm, with no particles >3 μ.

Pharmacodynamics in Rats

Sprague-Dawley rats (400–600 g) were anesthetized, and anesthesia maintained with halothane 1.5% in 100% oxygen with spontaneous ventilation via a Fluo-Vac® system (International Market Supply, Cheshire, UK). The femoral artery and vein were cannulated and arterial blood pressure was continuously monitored. The operating table functioned as a stable platform to which the rat was secured and the transducer was attached. The left forelimb was fixed by placing it through the cut barrel and stopper of a 10-mL syringe so that adduction could be measured via strain-gauge transducer (5). The baseline tension was set at 2 g. Needle electrodes, 27 gauge, were used to locate the median nerve high in the axilla and between the epicondyles of the humerus. Optimal voltage of electrical stimulation was determined when twitch response no longer increased with increasing voltage (3–5 V applied for a duration of 0.02 ms). The stimulating voltage was then doubled to ensure maximal stimulation and the frequency was set at 0.2 Hz. The baseline and twitch tensions were considered stable when they varied less than 0.1 g over 10 min. The rats were randomized into one of three groups: saline control (n = 6), D (n = 5), or MC-NaD (n = 6). A dose-response was obtained by administering D or MC-NaD (0.33 mg/mL) at 0.15 mg/kg IV or a matched saline volume at 2-min intervals via the femoral vein catheter to a total dose or saline matched volume of 4 mg/kg.

Pharmacokinetics in Rats

The anesthetic technique and catheter placement were similar to the pharmacodynamic preparation, with the exception that the catheters were tunneled subcutaneously to the posterior neck. After recovery from the anesthetic, the rats were randomized into two groups, D pharmacokinetics (D_K) (n = 4) and MC-NaD pharmacokinetics (MC-NaD_K) (n = 5). The 95% effective dose (ED_{95}) (2.8 mg/kg), as determined from the pharmacodynamic data, was injected over 3 min. Arterial blood samples, 0.3 mL, were drawn at 10, 20, 30, 60, 180, 360, 600, and 1440 min postinjection. The plasma was separated and frozen at −70°C until assayed.

The plasma dantrolene assays were performed as described by Peterson and Lalande (6) with minor modifications. Pharmacokinetic parameter estimates were determined using MKMODEL® (Version 5, Biosoft®, Cambridge, UK). The area under the concentration curve was calculated using the trapezoidal method from Time 0 to the last concentration time point. The volume of distribution (V) and clearance (CL) parameter estimates were determined by fitting time/concentration data to a one-compartment bolus infusion model, the model which gave the best fit. The following equation:

$$t_{1/2} = (0.693 \cdot V)/CL$$

was used to calculate half-life.

Pharmacodynamics in Swine

Yorkshire swine (15–20 kg) were anesthetized with thiopental, 5–10 mg/kg IV, through a previously placed central catheter. The swine were tracheally intubated and mechanically ventilated to maintain $ETco_2$ at 40 ± 5 mm Hg. End-tidal halothane was maintained at 1% (Datex, Helsinki, Finland). The left forelimb was fixed similar to the method described by Flewellen and Nelson (2) to quantify adduction. The baseline tension was set at 10 g, otherwise the procedure was the same as described above for the rats. Each swine received D or MC-NaD in a random fashion. After a minimum 4-day recovery period, the experiment was repeated using the other dantrolene formulation. The dose-response was obtained by administering D (n = 5) or MC-NaD (n = 5), 0.15 mg/kg IV, at 2-min intervals (7). Controls (n = 3) received a saline equivalent volume at 2-min intervals.

In a separate group of Yorkshire swine (15–20 kg) the pharmacodynamics of MC-D was obtained. The method was identical to the previous group with the following exceptions: The swine were sedated with

ketamine, 10 mg/kg intramuscularly, to allow for induction of anesthesia via an ear vein catheter and a pulmonary artery catheter was placed via the right internal jugular vein. The dose-response was obtained by administering MC-D (n = 4), 0.25 mg/kg IV, at 2-min intervals. A matching group for D pharmacodynamics (n = 4) was also studied.

MC-NaD Pretreatment and Treatment Challenge in MHS Swine

The effectiveness of MC-NaD pretreatment in preventing MH was determined in the following manner in four MHS swine: For this experiment, minute ventilation was held constant and MH/failure was defined as a sustained increase of $ETco_2$ > 50 mm Hg. Arterial blood pressure was continuously monitored via a previously positioned carotid artery catheter. MHS swine (Pietrain 25–50 kg) were administered an ED_{95} dose of filtered (6 μ) MC-NaD, 2.85 mg/kg IV bolus, through a previously positioned central catheter. Anesthesia was induced via a mask with halothane, 5% in oxygen, 30 min after MC-NaD was administered. After anesthetic induction, the swine were tracheally intubated and a constant ventilation (100 mL · kg^{-1} · min^{-1}) was maintained. Heart rate, respiratory rate, $ETco_2$, end-tidal halothane, and rectal temperature were monitored continuously. Serial arterial blood gas data were also obtained. Mean arterial blood pressure was maintained above 60 mm Hg by regulating the inspired halothane concentration. If MH was not evident after 30 min of halothane exposure, succinylcholine, 2 mg/kg IV bolus, was administered and halothane was continued for an additional 30 min. If there was still no evidence of MH, MC-NaD was considered successful in preventing MH, halothane was discontinued, and the swine was allowed to recover.

Treatment challenge was conducted in the following manner in six MHS swine: Anesthesia was induced with propofol through a previously placed central catheter. After endotracheal intubation, controlled ventilation was maintained at 100 mL · kg^{-1} · min^{-1}. Arterial blood pressure, heart rate, respiratory rate, $ETco_2$, end-tidal halothane, and rectal temperature were monitored continuously. Skeletal muscle rigidity was graded as absent, mild, moderate, or severe. The halothane vaporizer was maintained at 3% until end-tidal halothane was more than 1.5% for at least 5 min. Succinylcholine, 2 mg/kg IV, was then administered and end-tidal halothane was reduced to 1%. As the $ETco_2$ began to increase, minute ventilation was increased to 300 mL · kg^{-1} · min^{-1} in order to maintain $ETco_2$ below 45 mm Hg. The diagnosis of MH was made when at least two of the following were observed: $ETco_2$ > 90 mm Hg, pH_a < 7.0, base excess > −9 mEq/L, or severe rigidity. Once the diagnostic criteria were met, three swine each were treated with either unfiltered (8) or filtered (6 μ) MC-NaD, 2.85 mg/kg IV bolus. End-tidal halothane remained at 1% and no other therapy was administered. Succinylcholine, 2 mg/kg IV, was repeated between 40 and 60 min after treatment. If there was no evidence of recrudescence of MH, the treatment was considered successful and the swine was allowed to recover.

Pulmonary Artery Pressure Response to MC-D in Dogs

The pulmonary artery pressure (PAP) response to MC-D was determined in three mongrel dogs (18–22 kg). After the placement of an IV catheter, anesthesia was induced with propofol and ventilation was controlled after endotracheal intubation. The anesthetic was maintained with propofol infusion, 300 μg · kg^{-1} · min^{-1} IV, or halothane 1%. Pulmonary artery catheters were placed via the right femoral vein. The dogs were challenged in the following manner with a 5-min observation period between doses: 1) filtered (6 μ) MC-D, 2.5 mg/kg IV bolus; 2) unfiltered MC-D, 2.5 mg/kg IV bolus; 3) unfiltered MC-D, 5 mg/kg IV bolus; and 4) unfiltered MC-D, 10 mg/kg IV bolus. The challenge would stop if any changes in PAP were observed.

All data are presented as mean ± SD. Statistical significance ($P < 0.05$) was determined using analysis of variance (factorial, *post hoc* test: Fisher's protected least significant difference), or Student's t-test.

Results

MC-NaD in Rats

Unfiltered MC-NaD (n = 6) was as effective as D (n = 5) in blocking indirect toe twitch (Figure 1). The groups were not significantly different for weight, total fluid administered, baseline tension, or twitch height tension. Pre- and postarterial blood gas analyses were not statistically different between the groups. The 50% effective dose (ED_{50}), ED_{95}, and total twitch depression for D and MC-NaD were similar (Table 1). These values compared favorably with those reported in MHS swine (2,3).

There were no statistically significant differences in the pharmacokinetic parameter estimates between D_κ and unfiltered MC-NaD_κ (Figure 2). Serum dantrolene concentrations were similar and consistent with published concentrations (4,9,10). There was no statistical difference between the two pharmacokinetic groups for weight or fluid administered. The mean area under the curve for D_κ and MC-NaD_κ was 1151 ± 245 and 1381 ± 563 μg · mL^{-1} · min^{-1}, respectively. The mean volumes of distribution for D_κ and MC-NaD_κ were 0.59 ± 0.11 and 0.54 ± 0.19 L/kg, respectively. The

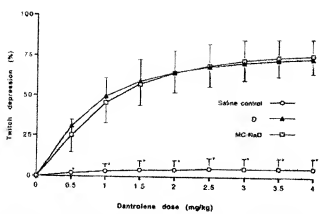

Figure 1. Dose response of lecithin-coated microcrystals of sodium dantrolene (MC-NaD) (n = 6), Dantrium® (D) (n = 5), and saline control (n = 6) for twitch depression in rat. Values are mean ± SD. *P < 0.05 for MC-NaD versus saline control and D versus saline control.

mean clearance was 2.288 ± 0.507 mL · min^{-1} · kg^{-1} for D_κ and 2.132 ± 0.791 mL · min^{-1} · kg^{-1} for MC-NaD_κ. The half-lives were 3.1 ± 0.8 h for D_κ and 3.1 ± 1.0 h for MC-NaD_κ. No adverse effects to MC-NaD were noted in awake or anesthetized rats.

MC-NaD in Normal Swine

In normal swine, unfiltered MC-NaD (n = 5) was as effective as D (n = 5) in blocking indirect forelimb twitch (Figure 3). The ED_{50}, ED_{95}, and total switch depression for D and MC-NaD were similar (Table 1). These values compared favorably with the rat data and those reported in MHS swine (2,3). In one swine, MC-NaD (0.15 mg/kg IV bolus) administration resulted in cardiovascular collapse that was refractory to all resuscitation efforts. In this animal $ETco_2$ decreased to 0 mm Hg within 2 min of MC-NaD administration. Pulmonary embolism was suspected as the cause of the cardiovascular collapse; however, postmortem examination showed no evidence of a large embolus.

This adverse event prompted a review of all data and monitoring procedures in the swine. Two other swine were found to have had a transient decrease in $ETco_2$ without hemodynamic compromise after the initial doses of MC-NaD. Particle-size analysis of the MC-NaD preparation was performed to determine whether microemboli or undissolved dantrolene could be responsible (particle size is directly related to fraction of undissolved drug release). Upon 200 × dilution, 19% of the MC-NaD participated in aggregates with diameters greater than 3 μ (ideal, 95% < 1 μ). Pulmonary artery catheter monitoring was used to further investigate this finding.

Unfiltered MC-NaD, 2.5 mg/kg IV bolus, was administered to two anesthetized swine and resulted in systemic hypotension with PAP exceeding normal systemic pressure. A similar response was seen when undissolved dantrolene powder was administered. When filtered (6 μ) MC-NaD, 2.5 mg/kg IV bolus, was administered to two additional anesthetized swine, PAP doubled with no change in systemic pressure. PAP peaked 2–4 min postinjection and gradually returned to baseline values over 60 min. Reformulation and 2 μ filtration did not eliminate increases in PAP after MC-NaD administration.

MC-D in Normal Swine

In normal swine, unfiltered MC-D (n = 4) was significantly less effective than D (n = 4) in blocking indirect forelimb twitch at doses up to 2.5 mg/kg (Figure 4). However, there was no significant difference in the dose response for twitch depression between D and MC-D above 2.5 mg/kg. Likewise, the ED_{50} was significantly different between the two groups, while the ED_{95} and total twitch depression were not significantly different (Table 1).

During the 40-min dose response, PAP increased to a similar degree in D swine (n = 2) and unfiltered MC-D swine (n = 4) (Table 2). An additional dose of unfiltered MC-D, 2.5 mg/kg IV bolus, was administered at the end of the dose response evaluation in the four MC-D swine. PAP peaked 4 min after MC-D administration with a mean increase in systolic and diastolic pressure of 8 and 5 mm Hg, respectively. PAP returned to baseline values within 10 min. Since PAP increased after bolus administration of unfiltered MC-D in these swine, filtered (2 μ) MC-D, 2.5 mg/kg IV bolus, was administered to three other swine. The effects on PAP were minimal (Table 2).

MC-D in Dogs

PAP did not change with the administration of filtered or unfiltered MC-D in doses up to 10 mg/kg, rapid IV bolus.

MC-NaD in MHS Swine

When filtered (6 μ) MC-NaD, 2.85 mg/kg IV bolus, was administered 30 min prior to exposure to halothane and succinylcholine, it was effective in the preventing MH in three of four MHS swine. No adverse effects or changes in systemic blood pressure were observed when MC-NaD was administered. However, PAP was not monitored.

The failed pretreatment was unlikely to be the result of inadequate drug delivery, since the plasma dantrolene concentration (4.2 μg/mL) in that swine was well above the concentration considered protective for MHS patients (2.4–2.8 μg/mL) (4). Although the pretreatment was unsuccessful in preventing MH, it slowed the progression of the episode (i.e., the

Table 1. ED_{50}, ED_{95}, and Percent Twitch Depression of Dantrolene Formulations in Rats, Normal Swine, and Malignant Hyperthermia Susceptible (MHS) Swine

Species	Formula	*n*	Total dose (mg/kg)	Incremental dose (mg/kg)	ED_{50} twitch depression (mg/kg)	ED_{95} twitch depression (mg/kg)	Percent twitch depression
Rat	MC-NaD	6	4	0.15	0.8 ± 0.2	2.6 ± 0.7	63 ± 4*
	Dantrium®	5	4	0.15	0.6 ± 0.1	2.8 ± 0.5	58 ± 3*
	Control	6	4	0.15			6 ± 2
Normal swine	MC-NaD	5	4	0.15	0.9 ± 0.3	2.8 ± 0.4	75 ± 10*
	Dantrium®	5	4	0.15	0.7 ± 0.3	2.7 ± 0.6	73 ± 9*
	Control	3	4	0.15			5 ± 6
Normal swine	MC-D	4	5	0.25	1.0 ± 0.2†	3.5 ± 0.4	74 ± 2
	Dantrium®	4	5	0.25	0.6 ± 0.1†	2.7 ± 0.5	83 ± 11
MHS swine[a]	Dantrolene[b]	6	2	0.15	0.85		68
	Dantrolene[c]	4	7.5	0.5		3.5	93

Values are mean ± SD.
MC-NaD = lecithin-coated microcrystals of sodium dantrolene; MC-D = lecithin-coated microcrystals of neutral dantrolene; ED_{50} and ED_{95} = 50% and 95% effective concentration, respectively.
[a] Data in MHS swine is presented for comparison.
[b] From Nelson and Flewellen (2).
[c] From Flewellen and Nelson (3).
* Significant difference ($P < 0.05$) from control.
† Significant difference ($P < 0.05$) MC-D versus Dantrium®.

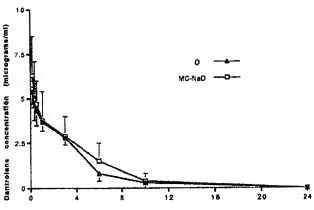

Figure 2. Plasma dantrolene concentrations for lecithin-coated microcrystals of sodium dantrolene (MC-NaD) ($n = 5$) and Dantrium® (D) ($n = 4$) in rat. Values are mean ± SD.

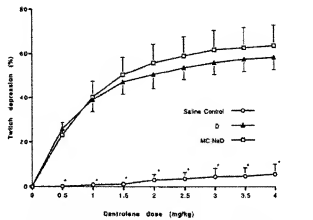

Figure 3. Dose response of lecithin-coated microcrystals of sodium dantrolene (MC-NaD) ($n = 5$), Dantrium® (D) ($n = 5$), and saline control ($n = 3$) for twitch depression in swine. Values are mean ± SD. *$P < 0.05$ for MC-NaD versus saline control and D versus saline control.

development of acidosis, temperature increase, and hypercarbia took much longer than when the swine were triggered during the treatment portion of the experiment).

When unfiltered or filtered (6 μ) MC-NaD, 2.85 mg/kg IV bolus, was used to treat MH episodes, it was successful in five of six MHS swine. The first five swine were triggered with succinylcholine while the last swine was triggered by halothane alone. The clinical expression of MH was distinctly different depending on the drug that triggered the episode. In the succinylcholine-triggered swine, $ETco_2$ quickly increased to more than 90 mm Hg despite a threefold increase in minute ventilation. Acidosis rapidly developed. Rigidity was a late finding and resolved within 2–3 min of MC-NaD treatment. All five animals triggered by succinylcholine were treated successfully and recovered without adverse sequela. Treatment was unsuccessful in the swine triggered by halothane alone. Rigidity occurred early in the episode. Acidosis and $ETco_2$ increase developed more slowly. By the time the diagnostic criteria for MH was met and treatment initiated, the rigidity was so severe that pulses could no longer be detected in the extremities, despite adequate central arterial pressures. It is unlikely that the skeletal muscle could achieve therapeutic dantrolene concentrations with perfusion compromised to this extent. Since the MH episode did not resolve despite multiple doses of both MC-NaD and D, treatment failure was thought to be the result of initiating treatment too late in the course of the episode.

Discussion

The results of this study show that lecithin-coated microcrystal technology can effectively deliver dantrolene to skeletal muscle in rats, normal swine, and MHS swine as measured by depression of skeletal muscle twitch height or the prevention and treatment of MH episodes. In addition, the MC-D formulation has greater potential to improve the pharmacologic treatment of MH due to its safety profile. The improvement in treatment is unusual, in that the delivery system is changed rather than the drug itself.

While lecithin-coated dantrolene eliminates the drawbacks of D (high pH, low solubility, cumbersome preparation, and limited access), it must also meet D's profile of safety and efficacy to be an acceptable treatment for MH. The only adverse effect noted in these experiments was pulmonary hypertension in swine after administration of MC-NaD. Our data suggest that the pulmonary response to MC-NaD was the result of undissolved dantrolene being release from MC-NaD.

The diameters of the lecithin-coated microcrystals in the preparation are vital in determining whether the pulmonary hypertensive response is elicited. Larger diameter particles appear to be responsible for the pulmonary response, but the exact mechanism is unknown. In theory, filtration should remove the larger particles that can be present as a byproduct of the manufacturing or the reconstitution process. However, filtration was not successful in eliminating the pulmonary response of MC-NaD in swine. Further observations at 200 × dilution showed a tendency for MC-NaD to aggregate even after filtration. We speculated that MC-NaD's tendency to aggregate was the result of a large dipole moment of the anionic form of dantrolene and predicted that aggregation would not be seen with MC-D, given its neutral form of dantrolene. Aggregation was not observed with MC-D at 200 × dilution. Unfiltered MC-D produced only mild increases of pulmonary artery pressure in swine. When MC-D was filtered with a 2-μ filter before administration, it did not produce pulmonary hypertension in swine. Additionally, when filtered or unfiltered MC-D was administered to dogs, no pulmonary response was detected. Although these results may suggest that the pulmonary responses to microcrystal preparations could be species specific, no firm conclusions can be made given the small number of animals examined. From the vantage of safety, MC-D is superior to MC-NaD.

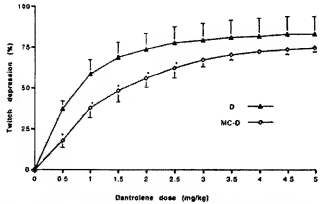

Figure 4. Dose response of lecithin-coated microcrystals of neutral dantrolene (MC-D) (n = 4) and Dantrium® (D) (n = 4) for twitch depression in swine. Values are mean ± SD. *$P < 0.05$ for MC-D versus D.

With regard to efficacy, MC-NaD is as effective as D in depressing muscular twitch height in rats and normal swine and in preventing or treating MH episodes in susceptible swine. Although MC-D's curve for the depression of muscular twitch height is shifted to the right of D in normal swine, the ED_{95} values were similar. Since dantrolene therapy is based on ED_{95}, we anticipate that MC-D will also be effective in the prevention and treatment of MH in susceptible swine. When considering both safety and efficacy, MC-D is the most likely candidate to improve the treatment of MH.

This drug trial is unusual in that it represents the first IV use of lecithin-coated microcrystal technology. As a result, the method of preparation and administration of the drug evolved as the experiments progressed to achieve a safer and more effective agent.

Table 2. Effects of Dantrolene Formulations on Pulmonary Artery Pressure (PAP) in Normal Swine

Dantrolene formulation	n	Dose (mg/kg)	No. of doses	Baseline PAP (mm Hg)	Peak/final PAP (mm Hg)
MC-D (unfiltered)	4	0.25	20	21 ± 2	23 ± 3
				13 ± 1	17 ± 2
Dantrium®	2	0.25	20	25 ± 0	29 ± 1
				20 ± 2	23 ± 1
MC-D (unfiltered)	4	2.5	1	23 ± 1	31 ± 8
				18 ± 2	23 ± 6
MC-D (2-μ filter)	3	2.5	1	20 ± 8	22 ± 6
				13 ± 8	15 ± 7

Values are mean ± SD.
MC-D = lecithin-coated microcrystals of neutral dantrolene.

However, this evolutionary process placed limits on the investigation as to the number of animals in any given experiment, the species tested, and microcrystal preparation investigated. The preparation was improved throughout the study, and the manufacturing process is currently being revised to achieve compliance with good manufacturing practice standards. In addition, lack of a standard commercial 2-μ filter limited our ability to determine a precise postfiltration drug concentration. Approximate concentrations were adequate for determining the effectiveness of MC-NaD in preventing or treating MH, but were not acceptable to conduct pharmacokinetic experiments in swine. Once it became evident that the pulmonary response to MC-NaD could not be overcome by filtration or reformulation, experiments designed to determine its efficacy in the prevention or treatment of MH were stopped. However, we believe that the lone treatment failure was not related to MC-NaD administration, since D also failed to reverse the episode. Rather, it is likely that treatment failure was due to initiating treatment too late in the course of the episode. Our treatment protocol was purposely designed to maximally test the lecithin-coated preparation by delaying treatment until the episode was severe and continuing the triggering drug during the treatment to eliminate the role of supportive care or removal of the triggering drug in reversing the MH episode. Finally, when it became evident that filtration would be necessary for the safe administration of MC-D, further experimentation was halted until a custom filter design was finalized.

This study suggests that MC-D may be successful in preventing and treating MH once good manufacturing practice standards are met and a custom filter is available. Further studies will determine MC-D's role in the treatment of MH. If successful, MC-D may significantly improve the treatment of MH by simplifying the administration of dantrolene, allowing the treatment of MH to begin more rapidly, and freeing the anesthesiologist to concentrate on the management of the patient.

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Review Article

Medical Progress

HEAT STROKE

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AND JAMES P. KNOCHEL, M.D.

HEAT stroke is a life-threatening illness characterized by an elevated core body temperature that rises above 40°C and central nervous system dysfunction that results in delirium, convulsions, or coma.[1] Despite adequate lowering of the body temperature and aggressive treatment, heat stroke is often fatal, and those who do survive may sustain permanent neurologic damage.[1,2] Data from the Centers for Disease Control and Prevention show that from 1979 to 1997, 7000 deaths in the United States were attributable to excessive heat.[3] The incidence of such deaths may increase with global warming and the predicted worldwide increase in the frequency and intensity of heat waves.[4-8]

Research performed during the past decade has shown that heat stroke results from thermoregulatory failure coupled with an exaggerated acute-phase response and possibly with altered expression of heat-shock proteins.[9-23] The ensuing multiorgan injury results from a complex interplay among the cytotoxic effect of the heat and the inflammatory and coagulation responses of the host.[9-21] In this article, we summarize the pathogenesis of heat stroke as it is currently understood and explore the potential therapeutic and preventive strategies. Key terms used in this discussion are defined in Table 1.

TABLE 1. GLOSSARY OF TERMS.

CONDITION	DEFINITION
Heat wave	Three or more consecutive days during which the air temperature is >32.2°C
Heat stress	Perceived discomfort and physiological strain associated with exposure to a hot environment, especially during physical work
Heat stroke	Severe illness characterized by a core temperature >40°C and central nervous system abnormalities such as delirium, convulsions, or coma resulting from exposure to environmental heat (classic heat stroke) or strenuous physical exercise (exertional heat stroke)
Heat exhaustion	Mild-to-moderate illness due to water or salt depletion that results from exposure to high environmental heat or strenuous physical exercise; signs and symptoms include intense thirst, weakness, discomfort, anxiety, dizziness, fainting, and headache; core temperature may be normal, below normal, or slightly elevated (>37°C but <40°C)
Hyperthermia	A rise in body temperature above the hypothalamic set point when heat-dissipating mechanisms are impaired (by drugs or disease) or overwhelmed by external (environmental or induced) or internal (metabolic) heat
Multiorgan-dysfunction syndrome	Continuum of changes that occur in more than one organ system after an insult such as trauma, sepsis, or heat stroke[24]

DEFINITION AND INCIDENCE

Heat stroke is defined clinically as a core body temperature that rises above 40°C and that is accompanied by hot, dry skin and central nervous system abnormalities such as delirium, convulsions, or coma. Heat stroke results from exposure to a high environmental temperature (in which case it is called classic, or nonexertional, heat stroke) or from strenuous exercise (in which case it is called exertional heat stroke).[1] On the basis of our understanding of the pathophysiology of heat stroke, we propose an alternative definition of this condition: it is a form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates.

Data on the incidence of heat stroke are imprecise because this illness is underdiagnosed and because the definition of heat-related death varies.[25,26] In an epidemiologic study during heat waves in urban areas in the United States, the incidence of heat stroke varied from 17.6 to 26.5 cases per 100,000 population.[26] Most people affected by classic heat stroke are very young or elderly, poor, and socially isolated and do not have access to air conditioning.[25,27] In Saudi Arabia, the incidence varies seasonally, from 22 to 250 cases per 100,000 population.[28] The crude mortality rate

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associated with heat stroke in Saudi Arabia is estimated at 50 percent.[28]

The incidence of heat exhaustion in Saudi Arabia, in contrast, ranges from 450 to more than 1800 cases per 100,000 population. Why a mild illness develops in response to heat (as in heat exhaustion) in some people, whereas in others the condition progresses to heat stroke, is unknown. Genetic factors may determine the susceptibility to heat stroke; candidate susceptibility genes include those that encode cytokines, coagulation proteins, and heat-shock proteins involved in the adaptation to heat stress.[13-22]

PATHOGENESIS

To understand the pathogenesis of heat stroke, the systemic and cellular responses to heat stress must be appreciated. These responses include thermoregulation (with acclimatization), an acute-phase response, and a response that involves the production of heat-shock proteins.

Thermoregulation

Body heat is gained from the environment and is produced by metabolism. This overall heat load must be dissipated to maintain a body temperature of 37°C, a process called thermoregulation.[1] A rise in the temperature of the blood by less than 1°C activates peripheral and hypothalamic heat receptors that signal the hypothalamic thermoregulatory center,[29] and the efferent response from this center increases the delivery of heated blood to the surface of the body. Active sympathetic cutaneous vasodilation then increases blood flow in the skin by up to 8 liters per minute.[30] An increase in the blood temperature also initiates thermal sweating.[31,32] If the air surrounding the surface of the body is not saturated with water, sweat will vaporize and cool the body surface. The evaporation of 1.7 ml of sweat will consume 1 kcal of heat energy.[32] At maximal efficiency in a dry environment, sweating can dissipate about 600 kcal per hour.[31-33] The thermal gradient established by the evaporation of sweat is critical for the transfer of heat from the body to the environment. An elevated blood temperature also causes tachycardia, increases cardiac output, and increases minute ventilation.[1,30-33] As blood is shunted from the central circulation to the muscles and skin to facilitate heat dissipation, visceral perfusion is reduced, particularly in the intestines and kidneys.[30] Losses of salt and water by sweating, which may amount to 2 liters or more per hour, must be balanced by generous salt supplementation to facilitate thermoregulation.[33,34] Dehydration and salt depletion impair thermoregulation.[34]

Acclimatization

Successive increments in the level of work performed in a hot environment result in adaptations that eventually allow a person to work safely at levels of heat that were previously intolerable or life-threatening.[1] The process of acclimatization to heat takes several weeks and involves enhancement of cardiovascular performance, activation of the renin–angiotensin–aldosterone axis, salt conservation by the sweat glands and kidneys, an increase in the capacity to secrete sweat, expansion of plasma volume, an increase in the glomerular filtration rate, and an increase in the ability to resist exertional rhabdomyolysis.[35]

Acute-Phase Response

The acute-phase response to heat stress is a coordinated reaction that involves endothelial cells, leukocytes, and epithelial cells and that protects against tissue injury and promotes repair.[36] Interleukin-1 was the first known mediator of the systemic inflammation induced by strenuous exercise.[37] A variety of cytokines are now known to be produced in response to endogenous or environmental heat (Table 2).[22,38-43,46-51] Cytokines mediate fever, leukocytosis, increased synthesis of acute-phase proteins, muscle catabolism, stimulation of the hypothalamic–pituitary–adrenal axis, and activation of leukocytes and endothelial cells.[22,51-53] The interleukin-6 produced during heat stress modulates local and systemic acute inflammatory responses by controlling the levels of inflammatory cytokines[22,51,54]; interleukin-6 also stimulates hepatic production of antiinflammatory acute-phase proteins, which inhibit the production of reactive oxygen species and the release of proteolytic enzymes from activated leukocytes.[36,51,54] Other acute-phase proteins stimulate endothelial-cell adhesion, proliferation, and angiogenesis, thus contributing to repair and healing.[36] The increased expression of the gene encoding interleukin-6 in human muscle cells, but not in blood monocytes, during the acute-phase response to exercise suggests that the onset of inflammation is local.[22,41,42] The systemic progression of the inflammatory response is secondary and involves other cells, such as monocytes.[41] A similar sequence of events has been shown to occur in sepsis.[55]

Heat-Shock Response

Nearly all cells respond to sudden heating by producing heat-shock proteins or stress proteins.[56,57] Expression of heat-shock proteins is controlled primarily at the level of gene transcription. During heat stress, one or more heat-shock transcription factors bind to the heat-shock element, resulting in an increased rate of transcription of heat-shock proteins.[56,57] Increased levels of heat-shock proteins in a cell induce a transient state of tolerance to a second, otherwise lethal, stage of heat stress, allowing the cell to survive.[23,56,57] Blocking the synthesis of heat-shock proteins either at the gene-transcription level or by specific antibodies

TABLE 2. EFFECT OF HEAT STRESS AND HEAT STROKE ON CIRCULATING CYTOKINES, CYTOKINE RECEPTORS, GROWTH FACTORS, AND CHEMOKINES.*

CYTOKINE OR FACTOR	HEAT STRESS			HEAT STROKE		REFERENCE
	EXERCISE-INDUCED	ENVIRONMENTAL	THERAPEUTIC†	CLASSIC	EXERTIONAL	
Tumor necrosis factor α	Increased or unchanged	Unchanged	Increased or unchanged	Increased or unchanged	Increased	Bouchama et al.,[11] Espersen et al.,[36] Robins et al.,[38] Camus et al.,[40] Ostrowski et al.,[43] Moldoveanu et al.,[42] Suzuki et al.,[45] Chang[44]
Interleukin-1β	Increased or unchanged	NA	Increased	Increased or unchanged	Increased	Camson and Kluger,[27] Robins et al.,[29] Ostrowski et al.,[43] Moldoveanu et al.,[42] Chang,[44] Bouchama et al.[45]
Interleukin-2	Decreased or unchanged	NA	Unchanged	NA	NA	Espersen et al.,[36] Robins et al.[39]
Interleukin-6	Increased	Increased	Increased	Increased	Increased	Robins et al.,[39] Moldoveanu et al.,[42] Suzuki et al.,[45] Chang,[44] Bouchama et al.,[46] Hammami et al.[49]
Interleukin-8	Increased	NA	Increased	NA	NA	Pedersen and Hoffman-Goetz,[22] Robins et al.,[39] Suzuki et al.[45]
Interleukin-10	Increased	Increased	Increased	Increased	NA	Pedersen and Hoffman-Goetz,[22] Robins et al.,[39] Suzuki et al.,[45] Bouchama et al.[46]
Interleukin-12	Increased or unchanged	NA	Unchanged	NA	NA	Pedersen and Hoffman-Goetz,[22] Robins et al.,[39] Suzuki et al.,[45] Akimoto et al.[48]
Interleukin-1–receptor antagonist	Increased	NA	NA	NA	NA	Pedersen and Hoffman-Goetz,[22] Ostrowski et al.,[43] Suzuki et al.[45]
Soluble interleukin-2 receptor	Increased	NA	NA	Increased	NA	Pedersen and Hoffman-Goetz,[22] Suzuki et al.,[45] Hammami et al.[49]
Soluble interleukin-6 receptor	NA	Increased	NA	Decreased	NA	Hammami et al.[49]
Soluble tumor necrosis factor receptors (p55 and p75)	Increased	Increased or unchanged	Increased	Increased	NA	Pedersen and Hoffman-Goetz,[22] Hammami et al.[49]
Interferon-γ	Increased or unchanged	NA	Unchanged	Increased	NA	Pedersen and Hoffman-Goetz,[22] Robins et al.,[39] Suzuki et al.,[45] Bouchama et al.[46]
Interferon-α	Increased or unchanged	NA	Unchanged	NA	NA	Suzuki et al.,[45] Viti et al.[50]
Granulocyte colony-stimulating factor	Increased	NA	Increased	NA	NA	Pedersen and Hoffman-Goetz,[22] Robins et al.,[39] Suzuki et al.[45]
Macrophage-inhibitor proteins	Increased	NA	Unchanged	NA	NA	Pedersen and Hoffman-Goetz,[22] Robins et al.[39]

*Data are from studies in human subjects. NA denotes data not available.

†Whole-body hyperthermia may be induced in cancer therapy.

renders the cells extremely sensitive to a minor degree of heat stress.[16,58] In vivo, cellular tolerance protects laboratory animals against hyperthermia, arterial hypotension, and cerebral ischemia.[15,16] The protection conferred against heat-stroke injury correlates with the level of heat-shock protein 72, which accumulates in the brain after the priming heat-shock treatment.[15,16] The mechanism by which heat-shock proteins protect cells may relate to their function as molecular chaperones that bind to partially folded or misfolded proteins, thus preventing their irreversible denaturation.[56] Another possible mechanism involves heat-shock proteins that act as central regulators of the baroreceptor-reflex response during severe heat stress, abating hypotension and bradycardia and conferring cardiovascular protection.[16]

Progression from Heat Stress to Heat Stroke

Thermoregulatory failure, exaggeration of the acute-phase response, and alteration in the expression of heat-shock proteins may contribute to the progression from heat stress to heat stroke.

Thermoregulatory Failure

The normal cardiovascular adaptation to severe heat stress is an increase in cardiac output by up to 20 liters

per minute and a shift of heated blood from the core circulation to the peripheral circulation.[30] An inability to increase cardiac output because of salt and water depletion, cardiovascular disease, or a medication that interferes with cardiac function can impair heat tolerance and result in increased susceptibility to heat stroke.[1]

Exaggeration of the Acute-Phase Response

It is possible that the gastrointestinal tract fuels the inflammatory response.[12,40,59-63] During strenuous exercise or hyperthermia, blood shifts from the mesenteric circulation to the working muscles and the skin, leading to ischemia of the gut and intestinal hyperpermeability.[12,30,59-63] There is abundant evidence of hyperpermeability during heat stress in animal models but much less evidence of this phenomenon in humans.[9,10,12,59-63] In rats, heat stress leads to increased metabolic demand and reduced splanchnic blood flow, which in turn induce intestinal and hepatocellular hypoxia; the hypoxia results in the generation of highly reactive oxygen and nitrogen species that accelerate mucosal injury.[12,59]

Intestinal mucosal permeability to iodine-125–labeled endotoxin increases in heat-stressed rats that have a core temperature of 45°C.[60] In heat-stressed primates, endotoxin from the gut enters the circulation at a core temperature of 40°C, and its concentration increases as the core temperature rises.[9,10] Endotoxemia may then cause hemodynamic instability and death. Administration of antiendotoxin antibodies before heat stress occurs attenuates hemodynamic instability and improves outcome, suggesting that endotoxin is involved in the progression from heat stress to heat stroke.[10] In humans, high concentrations of endotoxin, inflammatory cytokines, and acute-phase proteins are found in the blood after strenuous exercise.[12,40,61,62] Increased intestinal permeability occurs in athletes exercising at 80 percent or more of maximal oxygen consumption.[61]

In summary, in the model of heat stroke based on experiments in animals and observations in humans (Fig. 1), local and systemic insults associated with heat stress, such as splanchnic hypoperfusion, alter the immunologic and barrier functions of the intestines.[12,59-63] This alteration allows leakage of endotoxins, increased production of inflammatory cytokines that induce endothelial-cell activation, and release of endothelial vasoactive factors such as nitric oxide and endothelins.[9,10,12,63,64] Both pyrogenic cytokines and endothelium-derived factors can interfere with normal thermoregulation by raising the set point at which sweating is activated and by altering vascular tone, particularly in the splanchnic circulation, thereby precipitating hypotension, hyperthermia, and heat stroke.[9,10,12,63]

Alteration of Heat-Shock Response

Increased levels of heat-shock proteins protect cells from damage by heat, ischemia, hypoxia, endotoxin, and inflammatory cytokines.[23,56,57] In persons who are subjected to heat stress, examination of muscle tissue, blood monocytes, and serum reveals that such a heat-shock response occurs in vivo.[17,65-67] Attenuation of the heat-shock response during heat stroke suggests that this adaptative response is protective.[17,23] Conditions associated with a low level of expression of heat-shock proteins — for instance, aging, lack of acclimatization to heat, and certain genetic polymorphisms — may favor the progression from heat stress to heat stroke.[17,23,68]

PATHOPHYSIOLOGY

Heat stroke and its progression to multiorgan-dysfunction syndrome are due to a complex interplay among the acute physiological alterations associated with hyperthermia (e.g., circulatory failure, hypoxia, and increased metabolic demand), the direct cytotoxicity of heat, and the inflammatory and coagulation responses of the host.[11-15,18-21,44,45,69-72] This constellation of events leads to alterations in blood flow in the microcirculation and results in injury to the vascular endothelium and tissues (Fig. 2).[18,19,73-76]

Heat

Studies in cell lines and animal models suggest that heat directly induces tissue injury.[69,70] The severity of the injury depends on the critical thermal maximum, a term that attempts to quantify the level and duration of heating that will initiate tissue injury.[69-71] A critical thermal maximum beyond which near-lethal or lethal injury occurs has been determined in various mammalian species.[71] Observations in selected groups, including marathon runners, normal volunteers, and patients with cancer who are treated with whole-body hyperthermia, suggest that the critical thermal maximum in humans is a body temperature of 41.6°C to 42°C for 45 minutes to 8 hours.[71] At extreme temperatures (49°C to 50°C), all cellular structures are destroyed and cellular necrosis occurs in less than five minutes.[69] At lower temperatures, cell death is largely due to apoptosis.[70] Although the pathways of heat-induced apoptosis have not been identified, the induction of heat-shock proteins is protective.[57]

Cytokines

The plasma levels of inflammatory cytokines (tumor necrosis factor α [TNF-α], interleukin-1β, and interferon-γ) and antiinflammatory cytokines (interleukin-6, soluble TNF receptors p55 and p75, and interleukin-10) are elevated in persons with heat stroke; cooling of the body to a normal temperature does not result in the suppression of these factors.[11,44,45,47,49] The

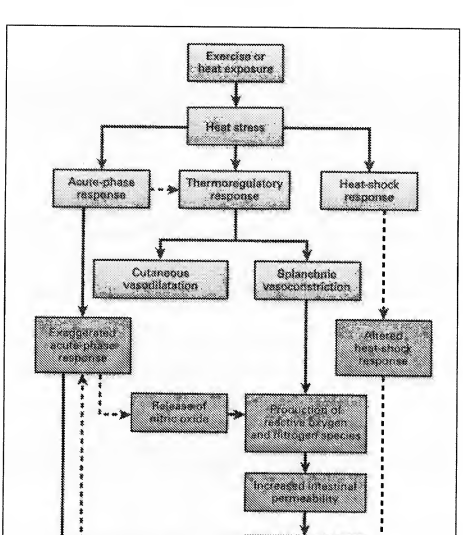

Figure 1. The Sequence of Events in the Progression of Heat Stress to Heat Stroke.

Heat stress induces thermoregulatory, acute-phase, and heat-shock responses. Thermoregulatory failure, exaggeration of the acute-phase response, and alteration in the expression of heat-shock proteins, individually or collectively, may contribute to the development of heat stroke. Active cutaneous vasodilatation and splanchnic vasoconstriction permit the shift of heated blood from the central organs to the periphery, from which heat is then dissipated to the environment. This change may also lead to splanchnic hypoperfusion and ischemia, resulting in increased production of reactive oxygen and nitrogen species, which may in turn induce intestinal mucosal injury and hyperpermeability. Endotoxins may then leak into the circulation and enhance the acute-phase response, leading to increased production of pyrogenic cytokines and nitric oxide. Both cytokines and nitric oxide can interfere with thermoregulation and precipitate hyperthermia, hypotension, and heat stroke. The solid arrows indicate pathways for which there is clinical or experimental evidence, and the broken arrows indicate putative pathways.

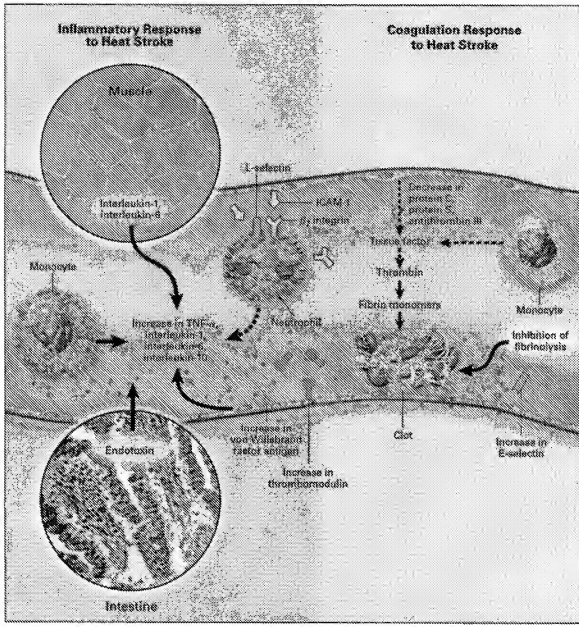

Figure 2. Possible Pathophysiological Mechanisms of Heat Stroke.

Hyperthermia due to passive heat exposure or to exercise may facilitate the leakage of endotoxin from the intestine to the systemic circulation as well as the movement of interleukin-1 or interleukin-6 proteins from the muscles to the systemic circulation. The result is excessive activation of leukocytes and endothelial cells, manifested by the release of proinflammatory and antiinflammatory cytokines (e.g., tumor necrosis factor α [TNF-α], interleukin-1, interleukin-6, and interleukin-10), up-regulation of cell-surface adhesion molecules, and shedding of soluble cell-surface adhesion molecules (e.g., E-selectin, L-selectin, and intercellular adhesion molecule 1 [ICAM-1]) as well as activation of coagulation (with decreased levels of proteins C and S and antithrombin III) and inhibition of fibrinolysis. The inflammatory and coagulation responses to heat stroke, together with direct cytotoxic effects of heat, result in injury to the vascular endothelium and microthrombosis. The solid arrows indicate pathways for which there is clinical or experimental evidence, and the broken arrows indicate putative pathways.

levels of interleukin-6 and TNF receptors correlate with severity of heat stroke.[45,49]

An imbalance between inflammatory and antiinflammatory cytokines may result in either inflammation-associated injury or refractory immunosuppression. Although dynamic studies of the cytokine response in patients with heat stroke have not yet been performed, both of these mechanisms may be important. In patients with heat stroke, the incidence of infection is high.[2] Studies in rats and rabbits have shown that heat stroke induces systemic and local (central nervous system) production of TNF-α and interleukin-1.[13,72] The increase in the levels of these inflammatory cytokines is associated with high intracranial pressure, decreased cerebral blood flow, and severe neuronal injury. Interleukin-1–receptor antagonists or corticosteroids given to animals before heat stroke attenuate neurologic injury, prevent arterial hypotension, and improve survival.[13,14] Although such studies support the possibility that cytokines have a pathogenic role, studies of neutralizing antibodies or genetically modified mice are needed to determine both the pattern and the role of these factors in heat stroke.

Coagulation Disorders and Endothelial-Cell Injury

Endothelial-cell injury and diffuse microvascular thrombosis are prominent features of heat stroke. Therefore, disseminated intravascular coagulation and alterations in the vascular endothelium may be important pathologic mechanisms in heat stroke.[18-21,73-76]

Studies involving the use of molecular markers of coagulation and fibrinolysis have delineated the early steps of coagulation abnormalities.[20,21] The onset of heat stroke coincides with the activation of coagulation, as assessed by the appearance of thrombin–antithrombin III complexes and soluble fibrin monomers and below-normal levels of protein C, protein S, and antithrombin III. Fibrinolysis is also highly activated, as shown by increased levels of plasmin–α_2-antiplasmin complexes and D-dimers and decreased levels of plasminogen. Normalization of the core temperature inhibits fibrinolysis but not the activation of coagulation, which continues; this pattern resembles that seen in sepsis.[20]

The endothelium controls vascular tone and permeability, regulates leukocyte movement, and maintains a balance between procoagulant and anticoagulant substances. Hyperthermia in vitro promotes a prothrombotic state, enhances vascular permeability, and increases the cell-surface expression of adhesion molecules and the shedding of their soluble form.[77,78] Circulating levels of von Willebrand factor antigen, thrombomodulin, endothelin, metabolites of nitric oxide, soluble E-selectin, and intercellular adhesion molecule 1 are elevated in patients with heat stroke.[18,19,53,64,79] Modulation of the expression of β_2-integrins, characterized by up-regulation of CD11b and down-regulation of CD11a on the surface of circulating lymphocytes, has been reported in patients with heat stroke, suggesting that there is an active endothelial cell–leukocyte interaction in vivo.[53]

CLINICAL AND METABOLIC MANIFESTATIONS

Two findings — hyperthermia and central nervous system dysfunction — must be present for a diagnosis of heat stroke (Table 3).[1,86] The core temperature may range from 40°C to 47°C.[1] Brain dysfunction is usually severe but may be subtle, manifesting only as inappropriate behavior or impaired judgment; more often, however, patients have delirium or frank coma.[1,86] Seizures may occur, especially during cooling.[1] All patients have tachycardia and hyperventilation. In either classic or exertional heat stroke, the arterial carbon dioxide tension is often less than 20 mm Hg.[1] Twenty-five percent of patients have hypotension.[86]

Patients with nonexertional heat stroke usually have respiratory alkalosis.[1] In contrast, those with exertional heat stroke nearly always have both respiratory alkalosis and lactic acidosis.[1] Hypophosphatemia and hypokalemia are common at the time of admission. Hypoglycemia is rare. Hypercalcemia and hyperproteinemia, reflecting hemoconcentration, may also occur. In patients with exertional heat stroke, rhabdomyolysis, hyperphosphatemia, hypocalcemia, and hyperkalemia may be important events after complete cooling.

The most serious complications of heat stroke are those falling within the category of multiorgan-dysfunction syndrome. They include encephalopathy, rhabdomyolysis, acute renal failure, acute respiratory distress syndrome, myocardial injury, hepatocellular injury, intestinal ischemia or infarction, pancreatic injury, and hemorrhagic complications, especially disseminated intravascular coagulation, with pronounced thrombocytopenia.[1,21]

TREATMENT

Immediate cooling and support of organ-system function are the two main therapeutic objectives in patients with heat stroke (Table 3).[1,2,80-87]

Cooling

Effective heat dissipation depends on the rapid transfer of heat from the core to the skin and from the skin to the external environment.[80-82] In persons with hyperthermia, transfer of heat from the core to the skin is facilitated by active cutaneous vasodilatation.[80,81,82] Therapeutic cooling techniques are therefore aimed at accelerating the transfer of heat from the skin to the environment without compromising

TABLE 3. MANAGEMENT OF HEAT STROKE.*

CONDITION	INTERVENTION	GOAL
Out of hospital		
Heat stress (due to heat wave, summer heat, or strenuous exercise), with changes in mental status (anxiety, delirium, seizures, or coma)	Measure the patient's core temperature (with a rectal probe)	Diagnose heat stroke†
	If the core temperature is >40°C, move the patient to a cooler place, remove his or her clothing, and initiate external cooling‡: cold packs on the neck, axillae, and groin; continuous fanning (or opening of the ambulance windows); and spraying of the skin with water at 25°C to 30°C	Lower the core temperature to <39.4°C, promote cooling by conduction, and promote cooling by evaporation
	Position an unconscious patient on his or her side and clear the airway	Minimize the risk of aspiration
	Administer oxygen at 4 liters/min	Increase arterial oxygen saturation to >90%
	Give isotonic crystalloid (normal saline)	Provide volume expansion
	Rapidly transfer the patient to an emergency department	
In hospital		
Cooling period	Confirm diagnosis with thermometer calibrated to measure high temperatures (40°C to 47°C)	
Hyperthermia	Monitor the rectal and skin temperatures; continue cooling	Keep rectal temperature <39.4°C§ and skin temperature 30°C–33°C
Seizures	Give benzodiazepines	Control seizures
Respiratory failure	Consider elective intubation (for impaired gag and cough reflexes or deterioration of respiratory function)	Protect airway and augment oxygenation (arterial oxygen saturation >90%)
Hypotension¶	Administer fluids for volume expansion, consider vasopressors, and consider monitoring central venous pressure	Increase mean arterial pressure to >60 mm Hg and restore organ perfusion and tissue oxygenation
Rhabdomyolysis	Expand volume with normal saline and administer intravenous furosemide, mannitol, and sodium bicarbonate	Prevent myoglobin-induced renal injury: promote renal blood flow, diuresis, and alkalization of urine
	Monitor serum potassium and calcium levels and treat hyperkalemia	Prevent life-threatening cardiac arrhythmia
After cooling	Supportive therapy	Recovery of organ function
Multiorgan dysfunction		

*Data are from Knochel and Reed,[1] Graham et al.,[40] Wyndham et al.,[41] Weiner and Khogali,[42] Al-Aska et al.,[43] White et al.,[44,45] and Boucharma et al.[46]

†Heat stroke should be suspected in any patient with changes in mental status during heat stress, even if his or her core temperature is <40°C.

‡There is no evidence that one cooling technique is superior to another. Noninvasive techniques that are easy to apply, well tolerated, and not likely to cause cutaneous vasoconstriction are preferred.

§There is no evidence to support a specific temperature end point at which cooling should be halted. However, a rectal temperature of 39.4°C has been used in large series and has proved to be safe.[46]

¶Hypotension usually responds to volume expansion and cooling. Vasodilatory shock and primary myocardial dysfunction may underlie sustained hypotension that is refractory to volume expansion. Therapy should be individualized and guided by the patient's clinical response.

the flow of blood to the skin.[80-85] This is accomplished by increasing the temperature gradient between the skin and the environment (for cooling by conduction) or by increasing the gradient of water-vapor pressure between the skin and the environment (for cooling by evaporation), as well as by increasing the velocity of air adjacent to the skin (for cooling by convection). In practice, cold water or ice is applied to the skin, which is also fanned (Table 4). Most such methods lower the skin temperature to below 30°C, triggering cutaneous vasoconstriction and shivering. To overcome this response, the patient may be vigorously massaged, sprayed with tepid water (40°C), or exposed to hot moving air (45°C), either at the same time as cooling methods are applied or in an alternating fashion.[80-85] There have been no controlled studies comparing the effects of these various cooling techniques on cooling times and outcome in patients with heat stroke.

No pharmacologic agents that accelerate cooling are helpful in the treatment of heat stroke. Although the use of dantrolene sodium has been considered, this agent was found ineffective in a double-blind, randomized study.[86] The role of antipyretic agents in heat stroke has not been evaluated, despite findings that pyrogenic cytokines are implicated in heat stress.

Recovery of central nervous system function during cooling is a favorable prognostic sign and should be expected in the majority of patients who receive prompt and aggressive treatment. Residual brain damage occurs in about 20 percent of the patients and is associated with high mortality.[1,2]

TABLE 4. METHODS OF COOLING.

Techniques based on conductive cooling
External*
  Cold-water immersion
  Application of cold packs or ice slush over part of the body or the whole body
  Use of cooling blankets
Internal†
  Iced gastric lavage
  Iced peritoneal lavage

Techniques based on evaporative or convective cooling
Fanning the undressed patient at room temperature (20°C to 22°C)
Wetting of the body surface during continuous fanning‡
Use of a body-cooling unit§

*Because external cooling results in cutaneous vasoconstriction, vigorous massaging of the skin is recommended.[41,42]

†Internal cooling, which has been investigated in animals, is infrequently used in humans.[44,45] Gastric or peritoneal lavage with ice water may cause water intoxication.

‡The skin is covered with a fine gauze sheet that has been soaked in water at 20°C while the patient is fanned. The fanning is reduced or stopped if the skin temperature drops to <30°C.[89]

§A body-cooling unit is a special bed that sprays atomized water at 15°C and warm air at 45°C over the whole body surface to keep the temperature of the wet skin between 32°C and 33°C.[82]

Prevention

Heat stroke is a preventable illness, and thorough knowledge of the disorder can help to reduce mortality and morbidity.[1,2] Although classic heat stroke is predominant in very young or elderly persons and in those who have no access to air conditioning,[1-3,25-27] it is also relatively common among persons with chronic mental disorders or cardiopulmonary disease and those receiving medications that interfere with salt and water balance, such as diuretics, antichoinergic agents, and tranquilizers that impair sweating.[1-3,25-27] Exertional heat stroke may be seen in manual laborers, military personnel, football players, long-distance runners, and those who ingest an overdose of cocaine or amphetamines.[1] To prevent both types of heat stroke, people can acclimatize themselves to heat, schedule outdoor activities during cooler times of the day, reduce their level of physical activity, drink additional water, consume salty foods, and increase the amount of time they spend in air-conditioned environments.[1,3] Automobiles should be locked, and children should never be left unattended in an automobile during hot weather.

Despite accumulated knowledge and experience, deaths during heat waves are still common[88-90] and have been associated largely with social isolation in vulnerable populations, lack of air conditioning, and increases in heat during large gatherings for cultural or religious purposes.[25-28,88-90] A plan to improve weather forecasting, alert those at risk, provide readily accessible air-conditioned shelters, and reduce energy costs during extreme weather so that air conditioning is affordable may decrease morbidity and mortality during heat waves.[88-90] In football players, modification of practice schedules and avoidance of dehydration and salt depletion have been found to be effective means of preventing heat stroke.[91]

Emerging Concepts

After the onset of heat stroke, normalizing the body temperature may not prevent inflammation, coagulation, and progression to multiorgan dysfunction.[1,11,18,20,45,49,52] For this reason, new approaches to modulation of the inflammatory response are being studied in animals. Immunomodulators such as interleukin-1–receptor antagonists, antibodies to endotoxin, and corticosteroids improve survival in animals but have not yet been studied in humans.[10,13,14] It is uncertain whether anticytokine and anti-endotoxin strategies will be more successful in heat stroke than they have been in sepsis. New therapeutic interventions aimed at limiting the activity of nuclear factor-κB, a critical transcription factor in the regulation of acute inflammation, may prove more successful: in a model of inflammation-associated injury (mice with sepsis), inhibition of nuclear factor-κB activity has been found to improve survival, but it also appears to promote apoptosis of hepatocytes.[92,93]

Coagulation and fibrinolysis are frequently activated during heat stroke and may lead to disseminated intravascular coagulation.[20,21] Replacement therapy with recombinant activated protein C, which attenuates both the coagulation and the inflammation, reduces mortality in patients with severe sepsis and may be useful in those with heat stroke as well.[20,94] Elucidation of the molecular mechanisms that trigger the activation of coagulation may lead to more specific therapy, such as tissue-factor pathway inhibitors.

More important are potential therapeutic applications based on knowledge of the stress-response proteins.[15,16] A logical goal for the next generation of immunomodulators is selective pharmacologic induction of the expression of heat-shock proteins. Salicylate and nonsteroidal antiinflammatory drugs activate heat-shock transcription factors and induce the transcription and translation of heat-shock proteins in mammalian cells.[57] This response enhances tolerance of heat and cellular protection against heat stress. Although excessive expression of the heat-shock proteins blocks essential cellular processes, partial up-regulation of these proteins may prove beneficial, particularly as a preventive measure during a heat wave. Further studies are required to define the degree to which inflammatory and stress responses can be modulated in humans without interfering with essential immunologic mechanisms.

CONCLUSIONS

The threat of heat stroke is increasing. Global warming is already causing heat waves in temperate climates.[4-8] The recognition that thermoregulatory failure and impaired regulation of inflammatory and stress responses facilitate the progression from heat stress to heat stroke and contribute to the severity of tissue injury should make research in this direction a priority. Greater knowledge of the cellular and molecular responses to heat stress will help point to novel preventive measures and a new paradigm of immunomodulation. In this way, the multiorgan injury caused by heat stroke might be minimized in many patients.

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1976-1985	Society of Neurosurgical Anesthesia and Neurologic Supportive Care
1985-1998	American Academy of Pediatrics, Section on Anesthesiology
1987-1998	American Trauma Society
1987-Present	Society for Pediatric Anesthesia
1987-1993	Society for Education in Anesthesia
1988 (elected to)	Association of University Anesthetists
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PUBLICATIONS

Refereed Articles.

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65. Brandom, BW, Larach MG: Reassessment of the safety and efficacy of dantrolene. ASA 2002 Annual Meeting, Abstract #650902

66. Woelfel SK, Brandom BW: Comparison of Acceleromyography (AMG) and Electromyography (EMG) for Monitoring Recovery of Neuromuscular Function in Pediatric Patients. ASA 2003 Annual Meeting, Abstract # 1123

67. Sambuughin N, Holley H, Brandom B, Nelson T, Muldoon S: Comprehensive screening of the RYR1 gene for malignant hyperthermia susceptibility. Barrow Neurological Institute, Phoenix, AR. ASA 2004 Annual Meeting Scientific Papers, #A-1603.

68. Brandom BW, Muldoon SM: Estimation of the incidence of malignant hyperthermia using a capture-recapture method in the USA. University of Pittsburgh Medical Center, Pittsburgh, PA. ASA 2004 Annual Meeting Scientific Papers, #A-1267.

69. Hoyer A, Veeser M, Schaupp F, Roewer N, Brandom BW. Low-dose dantrolene improves muscle function in walking MHS person. Wuerzburg, Germany. ASA 2004 Annual Meeting Scientific Papers, #A-1163.

70. Torp KD, Brandom BW, Capacchione JF, Voelkel ML, Muldoon SM. Caffeine halothane contracture test and ryanodine receptor type 1 analysis in patients who experienced MH episodes. ASA 2005 Annual Meeting Scientific Papers, #A-1273.

71. Sambuughin N, Brandom B, Capacchione J, Rosenberg H, Muldoon S. Toward updating the North American Malignant Hyperthermia Mutation Panel. ASA 2007 Annual Meeting Scientific Papers, #A503.

72. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Deaths associated with malignant hyperthermia (1987-2006) – A North American MH Registry of MHAUS Study. ASA 2007 Annual Meeting Scientific Papers, #A1031.

73. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Serious complications associated with malignant hyperthermia events – A North American MH Registry of MHAUS Study. ASA 2008 Annual Meeting Scientific Papers, to be submitted.

Letters:

1. Brandom BW, Cook DR: Dose response relationship to mivacurium in humans. Anesthesiology 70:1036-1037, 1989.

2. Brandom BW, Meretoja OA. Dose response calculations revisited. (Comment on Anesth Analg 77:164-167,1993) Anesth Analg 78:608-609, 1994.

3. Brandom BW, Westman HR: The effects of 0.86 mg/kg of cisatracurium in an infant. Anesthesiology 85:688-689, 1996.

4. Simhi E, Brandom BW: Cardiac output and onset time of different muscle relaxants. Anesth Analg 86:1145-1150, 1998.

5. Brandom BW, Muldoon SM: The practicality and need for genetic testing for malignant hyperthermia. Anesthesiology 103:1100; author reply 1101., 2005.

PROFESSIONAL ACTIVITIES

TEACHING:

I supervise student nurses, anesthesiology residents and fellows in pediatric anesthesiology during clinical care of all types of pediatric patients in the operating room at Children's Hospital. This accounts for about 60% of my working hours.

I participate in conferences at Children's Hospital in the Department of Anesthesiology and in the Didactic Lecture Series for the Anesthesiology Residents in the Departmetn of Anesheisology UPMC.

I give occasional lectures for educational programs in Children's Hospital such as:
November 3, 2007 Peri-Op Conference Basic Pharmacology of Analgesics

RESEARCH:

1. Grants Received (Years Inclusive), Grant Number and Title Source

1982	Efficacy and safety of atracurium in children and adolescents. Burroughs Wellcome Company, $22,495 Cook DR, Brandom BW, Woelfel
1983-1984	Blood-brain permeability to morphine in neonatal piglets. NIH-BRSG (HRC:CHP), $6,000 Brandom BW, Schieber RA, Cook DR
1983-1984	Safety and efficacy of atracurium in infant surgical patients under N_2O/O_2/halothane anesthesia. Burroughs Wellcome Company, $4,500 Cook DR, Brandom BW, Woelfel SK
1984	Kinetics of atracurium in children. Burroughs Wellcome Company, $7,200 Cook DR, Brandom BW, Woelfel SK, Stiller RL
1984	Efficacy and safety of atracurium infusions in pediatric surgical patients under N_2O/O_2 narcotic or halothane or isoflurane anesthesia. Burroughs Wellcome Company, $13,500 Cook DR, Brandom BW, Woelfel SK
1985	Comparison of succinylcholine and BW B1090U by infusion. Burroughs Wellcome Company, $18,000 Cook DR, Brandom BW, Weber S
1986-1987	Safety and efficacy of BW B1090U in adults. Burroughs Wellcome Company, $75,000 Cook DR, Brandom BW, Weber S, Powers DM
1986	In vivo degradation of BW B1090U and succinylcholine. Burroughs Wellcome Company, $25,000 Cook DR, Stiller RL, Brandom BW
1986-1987	Safety and efficacy of vecuronium at high doses. Organon Pharmaceutical, $36,000 Cook DR, Brandom BW, Stiller RL, Tullock WC
1987	Safety and efficacy of BW A938U in children. Burroughs Wellcome Company, $20,000 Brandom BW, Cook DR, Sarner JB, Woelfel SK
1987-1988	Safety and efficacy of BW B1090U in children. Burroughs Wellcome Company, $36,000 Brandom BW, Cook DR, Woelfel SK, Sarner JB
1988-1989	Determination of the cumulative dose-response of pipecuronium bromide in pediatric patients under halothane anesthesia. Organon Inc., $18,000 Brandom BW, Sarner JB, Dong ML

1990	A study of the safety and efficacy of ORG-9426 in pediatric surgical patients during nitrous oxide-oxygen-halothane anesthesia. AKZO, $27,000 Brandom BW, Woelfel SK, Sarner JB, Cook DR
1990	A study of the safety and efficacy of mivacurium (BW B1090U) in pediatric surgical patients during nitrous oxide-oxygen-halothane anesthesia. Burroughs Wellcome Co., $69,300 Brandom BW, Woelfel SK, McGowan FX, Cook DR
1991	A continuation of the study of the safety and efficacy of ORG-9426 in pediatric surgical patients during nitrous oxide-oxygen-halothane anesthesia. AKZO, $21,000 Brandom BW, Woelfel SK, McGowan FX, Cook DR
1993	A study of the safety and efficacy of BW 51W89 in pediatric surgical patients during nitrous oxide-oxygen-halothane anesthesia. Burroughs Wellcome Co, $33,660 Brandom BW, Woefel SK, Gronert BJ, Cook DR.
1994	Applied to the study of long-term infusion of doxacurium. Nonspecific support from Burroughs Wellcome Co., $1,000 Brandom BW.
1995	Effects of mivacurium 300 mcg/kg in pediatric surgical patients during nitrous oxide-oxygen-halothane or nitrous oxide-oxygen-narcotic anesthesia. Burroughs Wellcome Co., $76,140 Brandom BW, Woelfel SK, Gronert BJ, Simhi E.
1995	The use of neuromuscular blockers in the ICU. Glaxo Wellcome Inc., $1,500 Brandom BW.
1996	A study of the safety and efficacy of ORG-9487 in pediatric surgical patients during nitrous oxide-oxygen-halothane anesthesia. AKZO, $82,0082 Brandom BW, Simhi E, Woelfel SK, Lloyd M, Fertal K.
1996	Pharmacokinetics of doxacurium in pediatric patients undergoing laryngotracheoplasty and postoperative mechanical ventilation with cisatracurium administered during elimination of doxacurium. Glaxo Wellcome Inc., $6,076.37 Brandom BW, Woelfel SK, Lloyd M, Yellon RF, Venkataraman ST, Dohar JE, Post JC.
1997	An evaluation of the safety and efficacy of cisatracurium (Nimbex) for tracheal intubation in pediatric surgical patients during N2O/O2/halothane or N2O/O2/opioid anesthesia. Glaxo Wellcome Inc., $105,494 Brandom BW, Woelfel SK, Cook DR, Morillo-Delerme J.
1997	Comparison of Cisatracurium and Pancuronium in the Pediatric ICU. Glaxo Wellcome Inc., $20,726 Brandom BW, Venkataraman S, Thompson A, Cook DR.
1999	Invitro Metabolism of Rapacurium. Organon Inc., $35,000 Brandom BW, Carcillo J.
2000	Long-Term Infusion of Zemuron in Pediatric ICU Subjects. Organon Inc., $6,000 Brandom BW, Fine GF, Yellon RF, Landsman IS.
2000-2005	North American Malignant Hyperthermia Registry. Malignant Hyperthernia Association of the United States (MHAUS), $65,000/yr Brandom BW, Young M.
2006-2007	Multicenter evaluation of three doses of rocuronium in pediatric and adolescent subjects during anesthesia. Organon Inc, $303,000 Brandom BW, et al.
2005-2007	North American Malignant Hyperthermia Registry. Malignant Hyperthernia Association of the United States (MHAUS), $65,000/yr Brandom BW, Young M.
2007-2008	North American Malignant Hyperthermia Registry. Genetics of Malignant Hyperthermia (MHAUS), $70,000 Brandom BW, Muldoon SM.
2007-2009	North American Malignant Hyperthermia Registry. Malignant Hyperthernia Association of the United States (MHAUS), $87,000/yr Brandom BW, Young M.

2. Seminars and Invited Lectureships Related to Your Research:

April 1980	Brandom BW, Brandom RB, Cook DR: A mathematical model for predicting uptake and distribution in inhalation anesthetics in infants and children. This was presented in abstract form at the 1980 American Academy of Pediatrics, Section on Anesthesiology, April 1980, and at the 11th Annual Modeling and Simulation Conference at the University of Pittsburgh School of Engineering.
April 1980	Cook DR, Brandom BW, Shiu G: Brain halothane levels and halothane EDI50 in infant rats. Abstract presented at the 1980 American Academy of Pediatrics, Section on Anesthesiology meeting in Las Vegas, NV.
Oct. 14-16, 1980	Brandom BW: The microcomputer based model of inhalation anesthetic uptake and distribution was presented as a scientific exhibit at the American Society of Anesthesiologists meeting in St. Louis, MO.
Oct. 17, 1980	Brandom BW: An abbreviated discussion of the microcomputer based model of inhalation anesthetic uptake was delivered to the Microcomputers in Anesthseia conference in Iowa City, IO.
April 16, 1983	Brandom BW, Cook DR: Neuromuscular and cardiovascular effects of atracurium, gallamine, and pancuronium in pediatric patients during nitrous oxide- halothane anesthesia. Presented at the American Academy of Pediatrics meeting, Philadelphia, PA.
April 13, 1985	Brandom BW, Cook DR, Stiller RL: Pharmacokinetics of atracurium in infants and children. Presented at the American Academy of Pediatrics, Atlanta, GA.
April 30, 1987	Brandom BW: Preliminary Data on BW A938U and BW B1090U. Presented at the Third International Conference on Muscle Relaxants, Palm Springs, CA.
March 10, 1989	Theroux MC, Brandom BW: Neuromuscular monitoring of the flexor hallucis brevis versus the adductor pollicis in anesthetized children. Presented at the American Academy of Pediatrics meeting, Orlando, FL.
March 10, 1989	Brandom BW: The effects of fluids on nausea and vomiting in pediatric strabismus surgery patients. Presented at the American Academy of Pediatrics meeting, Orlando, FL.
March 17, 1991	Brandom BW, Woelfel SK, Sarner JB, Cook DR, Cyran JA: Dose-response of ORG-9426 in children during nitrous oxide-halothane anesthesia. Presented at the American Academy of Pediatrics Meeting, San Diego, CA.
March 17, 1991	Blinn A, Woelfel SK, Cook DR, Brandom BW, Cohen IT: Pancuronium dose-response revisited. Presented at the American Academy of Pediatrics Meeting, San Diego, CA.
May 25, 1992	Brandom BW, Woelfel SK, McGowan FX, Gronert BJ, Cook DR: Effects of ORG 9426 $600 \cdot mcg \cdot kg^{-1}$ in infants and children. 4th International Neuromuscular Symposium, Montreal, Quebec, Canada.
May 25, 1992	Brandom BW: Plasma cholinesterase activity and response to mivacurium in infants. Presented at the 4th International Neuromuscular Symposium, Montreal, Quebec, Canada.
April 23-25, 1994	Dayal B, Brandom BW, Woelfel SW, Gronert BJ, Cook DR, Ference A: 51W89 in Children During Halothane Nitrous Oxide Anesthesia. Presented at the American Academy of Pediatrics Section on Anesthesiology Program for Scientific Sessions, Denver, CO.

April 23-25, 1994 — Gronert BJ, Meretoja OA, Brandom BW, Woelfel SK, Cook DR: Synergism Between Pancuronium and Mivacurium. Presented at the American Academy of Pediatrics Section on Anesthesiology Program for Scientific Sessions, Denver, CO.

Feb. 17-19, 1995 — Taiwo OO, Woelfel SK, Brandom BW, Schoen HE, Gronert BJ, Cook DR: Spontaneous vs. edrophonium induced recovery from paralysis with mivacurium. Abstract presented at the 1st joint winter meeting of the Society for Pediatric Anesthesia and American Academy of Pediatrics Section on Anesthesiology, Phoenix, AZ.

Feb. 16-18, 1996 — Brandom BW, Meretoja OA, Simhi E, Taivainen T, Wolfe S, Woelfel SK, Gronert BJ, Cook DR: Effects of mivacurium 300 mcg/kg in pediatric surgical patients during nitrous oxide-oxygen-halothane or nitrous oxide-oxygen-narcotic anesthesia. Abstract presented at the 2nd joint winter meeting of the Society for Pediatric Anesthesia and American Academy of Pediatrics Section on Anesthesiology, Tampa, FL.

Feb. 16-18, 1996 — Brandom BW, Lloyd ME, Woelfel SK, Simhi E, Landsman IS: Comparison of the Datex electromyograph and paragraph monitorery from pancuronium in anesthetized children. Abstract presented at the 2nd joint winter meeting of the Society for Pediatric Anesthesia and American Academy of Pediatrics Section on Anesthesiology, Tampa, FL.

Feb. 12-15, 1998 — Brandom BW, Yellon RF, Lloyd ME, Tischler, B, Venkataraman ST: Recovery from cisatracurium given after days of doxacurium infusion in the pediatric intensive care unit. Abstract presented at the joint meeting sponsored by the Society for Pediatric Anesthesia, the American Academy of Pediatrics--Section on Anesthesiology and the Society for Education in Anesthesia, Phoenix, AZ.

Feb. 12-15, 1998 — Brandom BW, Bikhazi G, Ginsberg B, Kenaan CA, Woelfel SK, Margolis J, Ross A, Fonseca JJ, Dear G, Lloyd ME: Mivacurium compared with Org-9487 in children anesthetized with nitrous oxide-halothane. Abstract presented at the joint meeting sponsored by the Society for Pediatric Anesthesia, the American Academy of Pediatrics--Section on Anesthesiology and the Society for Education in Anesthesia, Phoenix, AZ.

Feb. 12-15, 1998 — Brandom BW, Bikhazi G, Ginsberg B, Kenaan CA, Woelfel SK, Margolis J, Ross A, Fonseca JJ, Dear G, Lloyd ME: Org-9487 in neonates, infants and toddlers anesthetized with nitrous oxide-halothane. Abstract presented at the joint meeting sponsored by the Society for Pediatric Anesthesia, the American Academy of Pediatrics--Section on Anesthesiology and the Society for Education in Anesthesia, Phoenix, AZ.

June 14, 2003 — Brandom BW, Heil A, Kumaran S, Sei Y, Sambuughin N: Clinical characteristics of a MHS family with a novel mutation in the C-terminal domain of the RYR1 gene. Abstract presented at the Xth International Workshop on Malignant Hyperthermia and 22nd Annual Meeting of the European MH Group. Brunnen, Switzerland.

May 20, 2005 — Muldoon SM ,Torp KD, Capacchione JF, Voelkel ML, Brandom BW. Caffeine halothane contracture test and ryanodine receptor type 1 analysis in patients who experienced MH episodes. 24th Annual Meeting of the European MH Group. Mainz, Germany.

April 9, 2006 — Brandom BW. Malignant Hyperthermia Update. Pediatric Anesthesia Update Symposium. Pittsburgh, PA.

3. Other Research Related Activities

Sabbatical Activities

May to July 1992 — Visitor at the Children's Hospital of Helsinki, Finland, with Dr. Olli Meretoja, the Chief of Anesthesiology/ICU at that hospital.

Meetings

October 1998	Attended the MH Biopsy Conference in Chicago, Illinois
1999-present	Attended MHAUS Board meetings and conferences on genetics of MH.
March 23-25, 2001	Hosted the MH Biospy Center Directors meeting in Pittsburgh, PA.
September 2007	Attended the MH Biopsy Center and Hotline Consultants Conference in Philadelphia, PA

Extra Departmental Lectures (from 1990):

Feb. 6, 1990	Pain Response in the Neonate. Anesthesiology Grand Rounds, Wilmington General Hospital, Wilmington, DE.
May 19, 1990	Controversies in the Use of Relaxants in Pediatric Patients. The Third Annual Symposium on the State of the Art in Muscle Relaxants, Atlantic City, NJ.
May 29, 1990	Neuromuscular Blocking Drugs in Pediatric Anesthesia and Current Questions in the Administration of Intravenous Fluids to Pediatric Patients. Annual Review Course in Anesthesia, McGill University, Montreal, Quebec, Canada.
Aug. 2, 1990	Neuromuscular Blocking Drugs in Pediatric Anesthesia. Department of Anesthesiology, University of California at Davis, Davis, CA
Nov. 29, 1990	Anesthesia for Pediatric Outpatients. St. Vincent Charity Hospital, Cleveland, OH
Jan. 14, 1991	Malignant Hyperthermia. Trauma Conference, Children's Hospital of Pittsburgh, Pittsburgh, PA.
April 8, 1991	Neuromuscular Blocking Drugs in Infants and Children; Fluid Management in Pediatric Patients: Special Considerations. Pediatric Trauma, Miami Comprehensive Review Course, Miami, FL.
May 13 & 14, 1991	Neuromuscular Blocking Drugs and Management of the 1991 Pediatric Trauma Patient. University of Illinois in Chicago and Michael Reese Hospital, Chicago, IL.
May 18, 1991	Advances in Pediatric Anesthesia: Matching the New Anesthetics with the New Relaxants. The 4th Annual Symposium on the State of the Art in Muscle Relaxants, Atlantic City, NJ.
Oct. 29, 1991	Pediatric Clinical Forum. American Society of Anesthesiologists Meeting, San Francisco, CA.
Nov. 1991	Anesthetic Management of Pediatric Trauma Patients. Southern Medical Association, Atlanta, GA.
Jan. 13, 1992	Neuromuscular Blocking Drugs in Pediatric Anesthesia. Medical College of Virginia, Richmond, VA.
May 24, 1992	ORG 9426 in Infants and Children. 4th International Neuromuscular Symposium, Montreal, Quebec, Canada.
Oct. 16, 1992	Age-related Differences in Response to Neuromuscular Blocking Drugs. Society for Pediatric Anesthesia Meeting, New Orleans, LA.
Nov. 1992	Controversies in the Use of Neuromuscular Blocking Drugs in Pediatric Anesthesia. Akron, OH.
Nov. 1992	Controversies in the Use of Neuromuscular Blocking Drugs in Pediatric Anesthesia. Children's Hospital of Detroit, Detroit, MI.

Dec. 11, 1992	New Neuromuscular Blocking Drugs. Anesthesia Symposium, University of Helsinki, Helsinki, Finland.
Feb. 8, 1993	Controversies in the Use of Neuromuscular Blocking Drugs. Grand Rounds, Vanderbilt University, Nashville, TN.
April 8, 1993	Controversies in the Use of Neuromuscular Blocking Drugs in Pediatric Anesthesia. St. John's Hospital, Health East Pediatric Anesthesia Symposium, Minneapolis, MN.
April 10, 1994	Reversal of Neuromuscular Block. University of Pittsburgh Anesthesia Update and CDQ Exam Review Course, Pittsburgh, PA.
May 18, 1994	Will Rocuronium Replace Succinylcholine? Sixth Annual Review of Neuromuscular Blocking Drugs, Atlantic City, NJ.
June 4, 1994	Some Serious Anesthesia Complications: Controversies in the Use of Succinylcholine. Regional Meeting of Malignant Hyperthermia Association of the United States (MHAUS), Pittsburgh, PA.
June 15, 1994	Neuromuscular Blocking Drugs (3 controversial ones) in Pediatric Anesthesia. Maricopa County Hospital, University of Arizona, Phoenix, AZ.
Sept. 20, 1994	Mivacurium, A Neuromuscular Blocker for Use in Anesthetized Adults and Children. Hamot Medical Center, Anesthesiology Department, Erie, PA.
Oct. 7, 1994	Recent Publications Regarding Neuromuscular Blocking Drugs: Succinylcholine, Mivacurium, Rocuronium. Children's Hospital of Philadelphia, Anesthesiology Grand Rounds, Philadelphia, PA.
Oct. 8, 1994	Problems in Experimental Design and Analysis of Clinical Studies in Pediatric Anesthesiology. The First Delaware Valley Pediatric Anesthesiology Consortium meeting, A.I. DuPont Institute, Wilmington, DE.
Oct. 16, 1994	Anesthesia for Gastrointestinal Emergencies in the Neonate and Infant. Fairview General Hospital, Cleveland, OH.
Dec. 13, 1994	Succinylcholine and the Federal Drug Administration. Post Graduate Assembly, New York, NY.
Jan. 10, 1995	Reversal of Neuromuscular Block. Department of Anesthesiology, Boston Children's Hospital, Boston, MA.
Jan. 11, 1995	Neuromuscular Blocking Drugs in Pediatric Anesthesia. Department of Anesthesiology, University of Massachusetts, Worcester, MA.
May 3, 1995	Neuromuscular Blocking Drugs in Pediatric Anesthesia. Department of Anesthesiology, Medical Center of Central Massachusetts, Worcester, MA.
May 7, 1995	Complications of Succinylcholine. 7th Annual Symposium on the State of the Art in Muscle Relaxants, Atlantic City, NJ.
June 8, 1995	Reversal of Neuromuscular Block. Department of Anesthesiology, University of California at Davis, Davis, CA.
June 8, 1995	Neuromuscular Blocking Drugs in Pediatric Anesthesia. Sacramento, CA.
Oct. 22, 1995	Muscle Relaxants in Infants and Children—How The Differ From Adults. ASA Refresher Course, Atlanta, GA.
Nov. 14, 1995	Intravenous Inductions in Pediatric Anesthesia. Augusta, GA.

Nov. 15, 1995	Neuromuscular Blocking Drugs in Pediatric Anesthesia. Department of Anesthesiology, Medical College of Georgia, Augusta, GA.
Nov. 16, 1995	Management of Pediatric Trauma. Department of Anesthesiology, Medical College of Georgia, Augusta, GA.
March 6, 1996	Intravenous Induction Techniques in Pediatric Anesthesia, and Special Considerations in Pediatric Trauma, 10th Annual Miami Comprehensive Review Course in Anesthesiology, Miami, FL.
April 17, 1996	Muscle Relaxants in Infants and Children—How They Differ From Adults. London, Ontario.
April 18, 1996	Neuromuscular Blocking Drugs in Pediatric Anesthesia. Toronto Academy of Medicine, Anesthesiology Section, London, Ontario.
Sept. 5, 1996	Neuromuscular Blockers and the ICU: What Do We Know? 5th Annual Pediatric Technology Conference of the Pediatric Pharmacy Advocacy Group, Inc. Scottsdale, AZ.
Nov. 16, 1996	Post Obstructive Pulmonary Edema, 3rd International Symposium on the Pediatric Airway, Orlando, FL.
Nov. 17, 1996	Post Operative Management of Infants after Larynngotracheal Reconstruction, 3rd International Symposium on the Pediatric Airway, Orlando, FL.
Jan. 16, 1997	Update in Pediatric Anesthesia, Primary Children's Hospital, Salt Lake City, UT.
Dec. 14, 1997	Neonatal Surgery: Gastroschisis, Omphalocoele, Tracheo-Esophageal Fistulae, Diaphragmatic Hernia. Anesthesia for Neonatal Emergencies, Post Graduate Assembly, New York, New York.
Feb. 25, 1998	Post Obstructive Pulmonary Edema, Medical College of Ohio Anesthesiology Department Visiting Professor, Toledo, Ohio.
June 6, 1998	Preparing for Outpatient Surgery for the Malignant Hyperthermia Susceptible Patient, MHAUS Regional Conference, Pittsburgh, PA
July 25, 1998	Mentoring, Panel Discussion on "What Does It Mean To Be A Clinical Educator" Education Retreat, Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA
Oct. 14-15, 1998	Post Obstructive Pulmonary Edema; Anesthesia for Neonatal Surgery: Gastroschisis, Omphalocoele, Tracheo-Esophageal Fistulae, University of Rochester, Rochester, New York, Anesthesiology Department Visiting Professor.
March 13, 1999	Neuromuscular Blocking Agents in Pediatric Patients, Symposium in Neuromuscular Blocking Agents in the New Millenium: Current Use-Future Trends, IARS Meeting, Los Angeles, CA
June 7, 1999	Useful Neuromuscular Pharmacology for the Anesthesiologist, University of West Virginia, Morgantown, WVA, Anesthesiology Department Visiting Professor
September 1999	Update on Neuromuscular Blocking Drugs for Pediatric Anesthesia. Shreveport, LA
September 1999	Update on Neuromuscular Blocking Drugs for Pediatric Anesthesia. New York Hospital, New York, New York
September 1999	Update on Neuromuscular Blocking Drugs for Pediatric Anesthesia. Department of Anesthesiology, New York University, New York, New York.

October 1999	Update on Neuromuscular Blocking Drugs for Pediatric Anesthesia. CRNA District meeting, Scranton, PA
November 18, 1999	Malignant Hyperthermia, Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, Pittsburgh, PA
February 26, 2000	Malignant Hyperthermia, CRNA Regional Meeting, Magee Women's Hospital, Pittsburgh, PA.
March 15, 2000	Neuromuscular Blockers of Shorter Duration in Pediatric Patients, Beaver Medical Center, Department of Anesthesiology, Beaver, PA.
October 18, 2000	Update on Pediatric Pharmacology. ASA Annual Meeting, San Francisco, CA.
January 2001	Neuromuscular Blocking Drugs, Anesthesiology Department, New York Medical College, Valhalla, NY.
June 2, 2001	Malignant Hyperthermia, Clinical Presentations, Second Annual Summer Anesthesia Seminar of the University of Pittsburgh School of Nursing.
September 19, 2001	Neuromuscular Blocking Drugs, Anesthesiology Department, Los Angeles Children's Hospital, Los Angeles, CA.
October 12, 2001	The North American MH Registry, the 15th Annual Society of Pediatric Anesthesia meeting, New Orleans, Louisiana.
Spring 2002	Rhabdomyolysis, Grand Rounds, Brownsville General Hospital, Brownsville, PA.
August 19, 2002	Malignant Hyperthermia, Grand Rounds at North Hills Passavant Hospital, PA.
January 9, 2003	Malignant Hyperthermia for the ENT Surgeon, Department of Otorhinlaryngology, Children's Hospital of Pittsburgh.
February 30, 2003	Journal Club on new papers in Malignant Hyperthermia, for the Department of Anesthesiology, West Virginia University, Morgantown, West Virginia.
March 6, 2003	Malignant Hyperthermia, Grand Rounds for the Department of Anesthesiology UPMC.
October 12, 2003	What is new in the Diagnosis and Treatment of Malignant Hyperthermia, Refresher course at the American Society of Anesthesiologists Annual Meeting, San Francisco, CA.
October 22, 2004	Anesthesia for the Patient with Neuromuscular Disease, Society for Pediatric Anesthesia Annual Meeting, Las Vegas, NV.
October 25, 2004	What is new in the Diagnosis and Treatment of Malignant Hyperthermia, Refresher course at the American Society of Anesthesiologists Annual Meeting, Las Vegas, NV.
November 13, 2004	Malignant Hyperthermia Update, Assembly of States Meeting American Association of Nurse Anesthetists, Miami, FL.
December 2, 2004	Malignant Hyperthermia 2004-2005, Department of Anesthesiolgy, UPMC, Pittsburgh, PA
February 9, 2005	What is new in the Diagnosis and Treatment of Malignant Hyperthermia, Department of Anesthesiology, Robert Wood Johnson Medical School
April 26, 2005	Genetics of Malignant Hyperthermia, The Center for Medical Genetics, Magee Women's Hospital, University of Pittsburgh Medical Center
August 27, 2005	Genetics of Malignant Hyperthermia, Anesthesiology Symposium, University of Pittsburgh Medical Center

October 2005	What is new in the Diagnosis and Treatment of Malignant Hyperthermia, Refresher course at the American Society of Anesthesiologists Annual Meeting, Atlanta, GA.
January 12, 2006	Complications with Succinylcholine, Grand Rounds, Department of Anesthesiolgy, UPMC, Pittsburgh, PA
January 26, 2006	A preventable death in the operating room? Clinical Genetics Case Conference, University of Pittsburgh Health Center, Pittsburgh, PA
February 15, 2006	Malignant Hyperthermia for Anesthesiology Residents, UPMC
February 17, 2006	Cases from the MH Hotline, Society for Pediatric Anesthesia, Sanibel Island, Florida
April 9, 2006	Malignant Hyperthermia in Pediatric Anesthesia, Pediatric Anesthesia Update Symposium, Children's Hospital of Pittsburgh, Pittsburgh, PA
February 13, 2006	Malignant Hyperthermia: What is New in Detection and Treatment. Memorial Sloan Kettering and New York Hospital, New York City, New York **CANCELLED for SNOW**

SERVICE:

1. University and Medical School:

1998	Ad Hoc Promotion Committee Chair for Howard A. Cohen, M.D. University of Pittsburgh School of Medicine
1999	Participated in the "Shadow Day Experience" of the Pennsylvania Governor's School for Health Care
2004-2010	Member, University of Pittsburgh Institutional Review Board (IRB)

2. Hospital / Departmental:

1980-Present	University Health Center of Pittsburgh, Children's Hospital: Coordinator of records and pre-op planning for patients susceptible to malignant hyperthermia.
1984-1985	Scientific Affairs Committee, Children's Hospital representative to Departmental Committee
1985-1986	Liason to tricyclic antidepressant studies at Western Pennsylvania Psychiatric Institute for facilitation of intravenous studies.
1987-1991	Acting Chief in absence of Dr. Cook, Children's Hospital.
1988-Present	Scientific Affairs Committee, Children's Hospital representative to the Departmental Committee
1989-1995	Disaster Preparedness Committee, Children's Hospital.
1989-1991	Internal coordinator of CA3 teaching program at Children's Hospital.
1990-2000	Pharmacy and Therapeutics Committee, Children's Hospital. Member of subcommittee on sedation guidelines.
1993-Present	Member of the Anesthesiology Pain Service at Children's Hospital. Presented discussion of Trigeminal Neuralgia, Sept. 3, 1997.

1993-Present	Trauma Medical Advisory Committee, Children's Hospital.
1993-Present	Trauma Steering Committee, Children's Hospital.
Fall 1994	Service Standards Committee Member, Children's Hospital.
Fall 1995	Chair, Committee on Issues of Discrimination, Department of Anesthesiology.
1996-2000	Chair, Pharmacy and Therapeutics Committee, Children's Hospital.
2000-present	Member, Pharmacy and Therapeutics Committee, Children's Hospital.
1999	Member, Search Committee for recruitment of a new Radiologist-in-Chief at Children's Hospital of Pittsburgh
1999-Present	Member, Department of Anesthesiology/Critical Care Medicine Reappointment and Promotion Committee.
August 2001-2002	Chair, Compensation Committee, Department of Anesthesiology.
2007-present	Member Risk Management for Clinical Studies Committee, Department of Anesthesiology.

3. National:

1986-1988	Committee on Pediatric Anesthesia of the American Society of Anesthesiologists, Meeting.
1988-1990	Member, Executive Committee (Drugs), Anesthesiology Section, American Academy of Pediatrics.
1989	Reviewed articles for The Journal of Pediatrics and Pediatric Pulmonology
1989-1991	Member, Executive Committee of the Anesthesiology Section of the American Academy of Pediatrics
1989-1992	Board of Directors, Society for Pediatric Anesthesia
1990-1991	Committee on Pediatric Anesthesia of the American Society of Anesthesiologists, Clinical
1991-1992	Sub-Committee on Pediatric Anesthesia for the American Society of Anesthesiologists, annual meeting
1991-present	Reviewer for Anesthesia and Analgesia
1991-present	MHAUS Hotline Consultant (Malignant Hyperthemia Association of the United States)
1992-1994	Member, Society for Pediatric Anesthesia, Committee on Research.
1992-present	Reviewer for Journal of Clinical Anesthesia
1993-present	Reviewer for Paediatric Anaesthesia
1993-1994	ASA Sub-Committee on Neuromuscular Transmission, Adjunct Member
1994	Reviewer for American Journal of Hospital Pharmacy

1994-2002	Reviewer for American Journal of Anesthesiology
1995-1996	ASA Committee on Pediatric Anesthesia
1996-present	Reviewer for American Journal of Health-System Pharmacy
March 1996	Moderator at the Society for Pediatric Anesthesia/Anesthesia Section of the American Academy of Pediatrics annual meeting.
Oct. 1996	Facilitator of a Pediatric Anesthesia Section and of a Neuromuscular Section of abstract presentations.
1997-present	Reviewer for Critical Care Medicine.
1998	Reviewer of thesis: Neuromuscular effects of anti-convulsant drugs, for Doctor of Philosophy candidate, Anhtung Nguyen, of The University of Sydney.
1998-2001	Chair of the Quality Assessment Committee for Review of Hotline Consultations, MHAUS
2000, 2005, 2007	Reviewer for Anesthesiology
2000-2008	ASA Sub-committee on Neuromuscular Transmission
2000-present	Reviewer for Pediatric Critical Care Medicine
2005-present	MHAUS Professional Advisory Council
2005-present	Editorial Board Member of Pediatric Anesthesia